
# CHIRAL AMINES *VIA* ASYMMETRIC REDUCTION OF IMINO BONDS

Thesis submitted in accordance with the requirements of the

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by

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To my grandparents

Pepa and Ángel

"If I find 10,000 ways something won't work, I haven't failed. I am not discouraged, because every wrong attempt discarded is another step forward"

Thomas Edison.

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# Abstract

Amines, in particular α–chiral amines, are highly valuable products and key intermediates of great importance in chemical synthesis. Therefore, developing new methods for the synthesis of optically pure amines is an important task in organic chemistry. Chapter 1 presents a general introduction to recent development in the asymmetric reduction of imino bonds, focusing on the metal-catalysed asymmetric hydrogenation of imines. This introduction will be followed by the presentation of several methodologies for the synthesis of amines, with an emphasis on chiral amines.

Chapter 2 describes the synthesis of α-chiral amines by direct reductive amination of ketones using $H_2$ as the hydrogen source. The catalyst is formed by the combination of a chiral Ir(III)-diamine complex and a chiral phosphate counteranion. We believe that the catalysis is brought about by the cooperative action of the metal and the counteranion, the former activating $H_2$ whilst the latter ion-pairing with the protonated substrate.

Chapter 3 describes the synthesis and characterization of several cyclometallated Ir(III)-imine complexes, and their application to imine hydrogenation. These cyclometallated iridium complexes are highly active for imine hydrogenation. Kinetic studies suggest that the hydrogen coordination to the metal centre is the rate-determining step.

Chapter 4 is a natural extension of Chapter 3. Chiral cyclometallated iridium complexes containing a chiral oxazoline ligand were applied to the asymmetric hydrogenation of imines using an *N*-benzylimine as a model substrate. The catalysts provide enantioselectivity up to 78% *ee*.

Chapter 5 presents the synthesis of β–chiral amines by a metal- and organo-catalysed hydroaminomethylation pathway. Styrene is selectively hydroformylated to the corresponding α-branched aldehyde with a Rh(I) complex, and subsequent reductive amination occurs with Hantzsch ester as the hydrogen source and a chiral phosphoric acid as the organocatalyst. Moderate yields and good enantioselectivities have been obtained.

# Publications

- **Hydrogenation of Imino Bonds with Half-Sandwich Metal Catalysts**
  Wang, C.; Villa-Marcos, B.; Xiao, J. *Chem. Comm.* **2011,** *47*, 9773-9785 (Feature article).

- **Bifunctional Catalysis: Direct Reductive Amination of Aliphatic Ketones with an Iridium-Phosphate Catalyst**
  Villa-Marcos, B.; Li, C.; Mulholland, K.R.; Hogan, P.J.; Xiao, J. *Molecules*, **2010**, *15*, 2453-2472.

- **Metal–Brønsted Acid Cooperative Catalysis for Asymmetric Reductive Amination**
  Li, C. Q.; Villa-Marcos, B.; Xiao, J. L. *J. Am. Chem. Soc.* **2009**, *131,* 6967-6969.
  * This work has been highlighted at: Klussmann, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 7124-7125.

- **Chiral Counteranion-aided Asymmetric Hydrogenation of Acyclic Imines**
  Li, C. Q.; Wang, C.; Villa-Marcos, B.; Xiao, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 14450-14451.

## Definitions and Abbreviations

| | |
|---|---|
| α | alpha |
| β | beta |
| δ | chemical shift |
| Å | amstrong |
| Ac | acyl |
| acac | acetylacetone |
| ACS | American Chemical Society |
| AOT | sodium bis(2-ethylhexyl)sulfosuccinate |
| aq | aqueous |
| Ar | aryl |
| ATH | asymmetric transfer hydrogenation |
| atm | atmosphere |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| Bn | benzyl |
| BDPCH | 1,2-cyclohexanol-bisdiphenylphosphinite |
| BDPP | 2,4-bis(diphenylphosphino)pentane |
| BOPA | *N,N,N*-bis(oxazolinylphenyl)amine |
| brs | broad singlet |
| Bu | butyl |
| °C | degree Celsius |
| CI | chemical ionisation |
| cm | centrimetre(s) |
| COD | 1,5-cyclooctadiene |
| conv. | conversion |
| Cp* | pentamethylcyclopentadienyl |
| Cy | cyclohexyl |
| d | doublet |
| DARA | direct asymmetric reductive amination |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |

| | |
|---|---|
| DDP | dipeptidyl peptidase |
| DDPPM | 1,4;3,6-Dianhydro-2,5-bis(diphenylphosphino)-dmannitol |
| DIOP | 2,2-dimethyl-4,5-(diphenylphosphino)dimethyldioxolane |
| DKR | dynamic kinetic resolution |
| DPEN | 1,2-diphenyl-1,2-ethylenediamine |
| DPPB | 1,4-Bis(diphenylphosphino)butane |
| DPPP | 1,3-Bis(diphenylphosphino)propane |
| DuanPHOS | 2,2′-Di-*t*Bu-2,3,2′,3′-tetrahydro-1*H*,1′*H*-(1,1′)biisophosphindolyl |
| *ee* | enantiomeric excess |
| eq | equivalent(s) |
| Et | ethyl |
| f-BINAPHANE | 1,1'-bisphosphanoferrocene |
| GCI | Green Chemistry Institute |
| GC-MS | gas cromathography-mass spectrometry |
| h | hour(s) |
| HEH | Hantzsch 1,4-dihydropyridine |
| Het | heterocyclic |
| HOMO | highest occupied molecular orbital |
| HPLC | high pressure liquid chromathography |
| HRMS | high resolution mass spectrometry |
| Hz | hertz |
| *i*Bu | 2-methylpropyl |
| IPHOS | 2,2'-bis((bis(3,5-bis(trifluoromethyl) phenyl)phosphino)methyl) -1,1'-binaphthyl |
| *i*Pr | isopropyl |
| IR | infrared |
| *J* | coupling constant value |
| kJ | kilojoules |
| *L* | levorotatory |
| LUMO | lowest unoccupied molecular orbital |
| *m* | meta |
| m | multiplet |

| | |
|---|---|
| Me | methyl |
| MEA | 2-methyl-5-ethylaniline |
| Me-DuPHOS | 1,2-Bis((2R,5R)-2,5-dimethylphospholano)benzene |
| mg | milligram(s) |
| MHz | megahertz |
| min | minute(s) |
| mL | mililitre |
| mmol | milimole(s) |
| mol | mole(s) |
| MONOPHOS | 3,5-Dioxa-4-phospha-cyclohepta[2,1;3,4]dinaphthalen-4yl)dimethylamine |
| MS | molecular sieves |
| MTBE | methyl*tert*-butyl ether |
| m/z | mass to charge ratio |
| NBD | norbornadiene |
| NBS | N-bromosuccinimide |
| nm | nanometre(s) |
| NMR | nuclear magnetic resonance |
| *o* | ortho |
| OAc | acetate |
| o/n | overnight |
| *p* | para |
| PCC | pyridinium chlorochromate |
| p-cymene | 1-methyl-4-(1-methylethyl)benzene |
| Ph | phenyl |
| Ph-BPM | 1,2-Bis(2,5-diphenylphospholano)methane |
| PHOX | phosphine oxazoline |
| PMP | *p*-methoxyaniline |
| PyBOX | bisoxazolinopyridine |
| PyOX | pyridinooxazoline |
| q | quatruplet |
| room | room temperature |

| | |
|---|---|
| temperature | |
| s | singlet |
| s | strong |
| SA | salicylate |
| S/C | substrate to catalyst ratio |
| SegPHOS | 5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole |
| SPO | secondary phosphine oxide |
| t | triplet |
| TBAI | tetrabutylammonium iodide |
| TBDMS | *tert*-butyldimethylsilyl |
| TBME | *tert*-butylmethylether |
| *t*Boc | *tert*-butyl carbonate |
| *t*Bu | *tert*-butyl |
| TFE | 2,2,2-trifluoroethanol |
| TH | transfer hydrogenation |
| THF | tetrahydrofuran |
| TOF | turnover frequency |
| Tol | *p*-methylphenyl |
| TON | turnover number |
| $t_R$ | retention time |
| Ts | *p*-methylbenzenesulfonyl |
| *vs* | *versus* |
| XANTPHOS | 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene |
| XYLIPHOS | 2-(diphenylphosphanyl)ferrocenylethyldi(3,5-xylyl)phosphane |

# Contents

# Chapter 1

# Introduction

## 1.1 Chiral amines

Amines, in particular α–chiral amines, are highly valuable products or key intermediates of great importance in organic chemistry. They are present in a vast number of bioactive compounds, with activities of relevance to agrochemical and pharmaceutical industries, and are used as versatile chiral ligands,[1-2] auxiliaries[3] or catalysts[4] in asymmetric catalysis.

Figure 1.1 outlines examples of chiral amines of commercial or academic interest. Chiral amine **1** is a building block for the herbicide metolachlor.[5] Tamsulosin, the active ingredient in the blockbuster drug Flomax, can improve symptoms in patients with chronic prostatitis.[6] Additionally, chiral cyclic amines, such as the tetrahydro-β-carboline moiety, frequently appear in natural products and biologically important molecules, like tubulosine displaying high antitumor activity.[7]

Chiral amines are widely present in asymmetric catalysis, displaying a variety of roles. In the field of asymmetric organocatalysis, amino catalysts have proven to be tremendously useful.[8-9] For instance, the natural amino acid *L*-proline has been shown to be an excellent catalyst for asymmetric intramolecular and intermolecular aldol reaction, and proceeds *via* an enamine intermediate.[10] In the role of ligand, a variety of monosulfonylated diphenylethylenediamines (DPEN) have been widely reported in transition metal complexes for asymmetric catalysis.[11] Whitesell developed the use of $C_2$-symmetrical chiral amines as chiral auxiliaries in 1977,[12] and they have been

extensively used since then.[13-14] For instance, diamine **2** performs asymmetric lactonisation reactions with high enantioselectivity.[15]

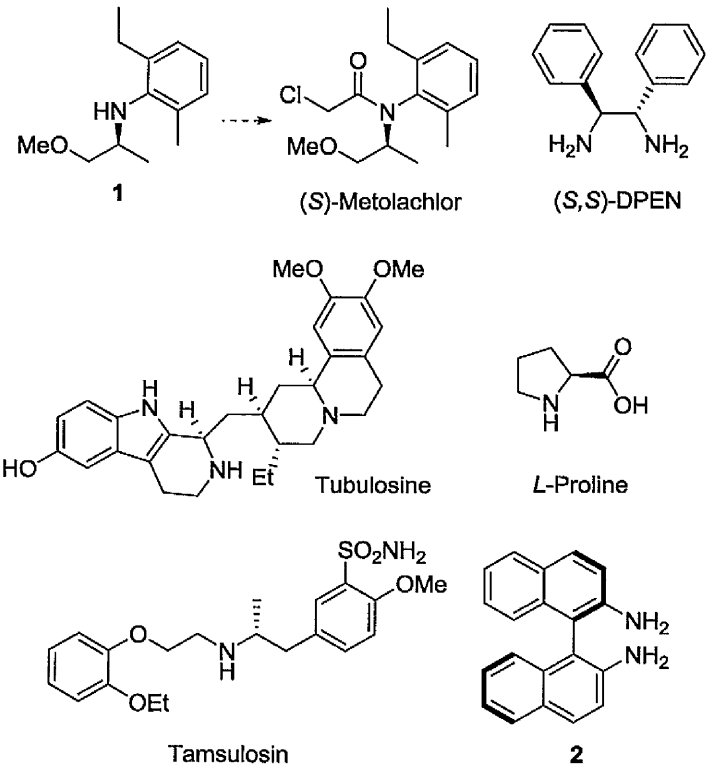


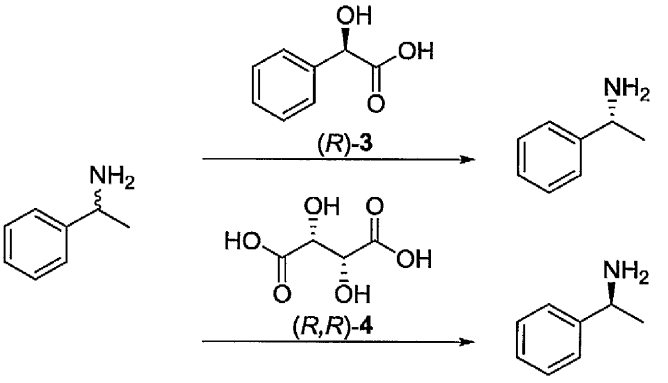

**Figure 1.1:** Examples of chiral amines used in agrochemical and pharmaceutical industries and in asymmetric catalysis.

## 1.2 Methods for chiral amine synthesis

Due to the importance of chiral amines as intermediates in pharmaceutical and agrochemical industries, several strategies have been developed for the synthesis of enantiomerically pure amines.[16] Here, an outline of some of the most successful methods, from a practical point of view, is presented.

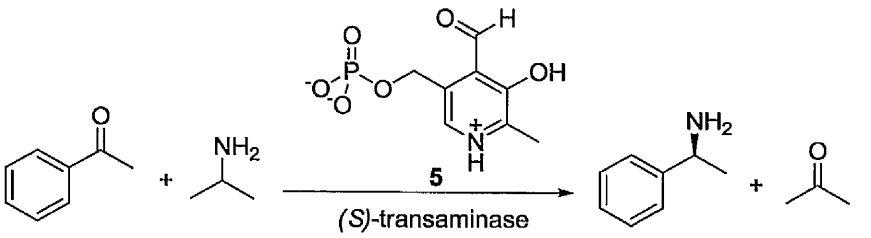
Amine enantiomers can be separated from a racemic mixture by formation and crystallisation of diastereomeric salts with chiral carboxylic acids, such as

((*R*)-mandelic acid **3** and (*R,R*)-tartaric acid **4**. Although the chiral carboxylic acid tends to be relatively inexpensive and may be recycled, a maximum of 50% can only be obtained for the desired enantiomer (Scheme 1.1).[16]



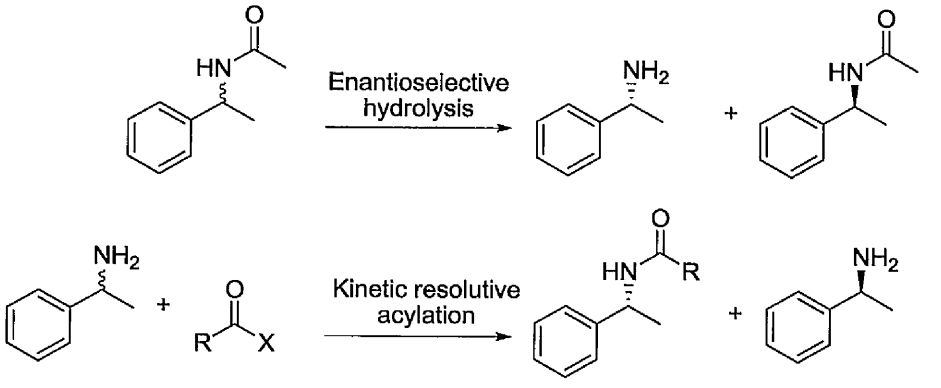

**Scheme 1.1**: Crystallization of diastereomeric salts with chiral carboxylic acids.

Transamination is a biotechnological process developed at Celgene in the 1980s for the synthesis of chiral amines.[16] An amino group is transferred to a prochiral ketone in the presence of enantioselective transaminases and the cofactor pyridoxal phosphate **5** (Scheme 1.2). Although both *R*- and *S*-selective transaminases have been developed, these enzymes are only effective in aqueous solution or in a mixture of organic-aqueous solution; so for those amine products only slightly soluble in water, very low concentrations of products are accomplished.



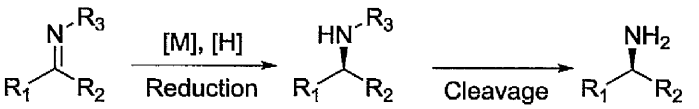

**Scheme 1.2:** Example of transamination dependent on cofactor **5**.

Both the enantioselective hydrolysis of amides and kinetic racemate resolution by acylation of amines have been reported in the literature as potential industrial biotechnological process for the synthesis of chiral amines, although the acylation has proven to be more successful (Scheme 1.3). Fu and co-workers developed a ferrocene derivative complex as the acylation catalyst for a series of aryl primary amines.[17] However, the combination of biocatalysts with acylation agents is still dominant on this kinetic resolution. Once again, the main drawback of these processes is the maximum yield being only 50% for the desired enantiomer.




**Scheme 1.3**: General scheme for enantioselective hydrolysis and synthesis of amides.

Asymmetric catalysis has also played an important role in the synthesis of chiral amines, although it is still in its infancy from an industrial point of view. Different approaches to chiral amines have been reported involving a chiral catalyst, e.g. Mannich reaction, hydrosilylation of imines, etc. However, the asymmetric catalytic hydrogenation of C=N double bonds has not been extensively developed in industry,[16] as there are only a few good catalysts reported (*vide infra*) (Scheme 1.4). This is partly due to difficulties in the synthesis and isolation of the imine, and cleavage of the frequently encountered *N*-aryl group to give primary amines.




**Scheme 1.4:** General method for the imine reduction leading to primary amine.

In comparison with that of ketone and olefin, the asymmetric hydrogenation of imines has been less explored. The main problems are:

- The net hydrogenation of C=N and C=O (~ -60 kJ/mol) is slightly less exothermic than C=C bond (~ -130 kJ/mol).[18]

- In case of substrate coordination to the metal centre, C=N and C=O bonds tend to exhibit the $\eta^1$-binding mode through the lone pair on the N or O atom, whereas olefins tend to prefer $\eta^2$-binding. $\eta^1$-Binding results in a less effective orbital overlap with the metal centre.

- In the case of imine hydrogenation, the amine product may coordinate to the metal complex, leading to a poisoning of the catalyst.

- The easy interconversion between *E*- and *Z*-isomers in solution for acyclic imines poses a problem for the achievement of high enantioselectivity.[19]

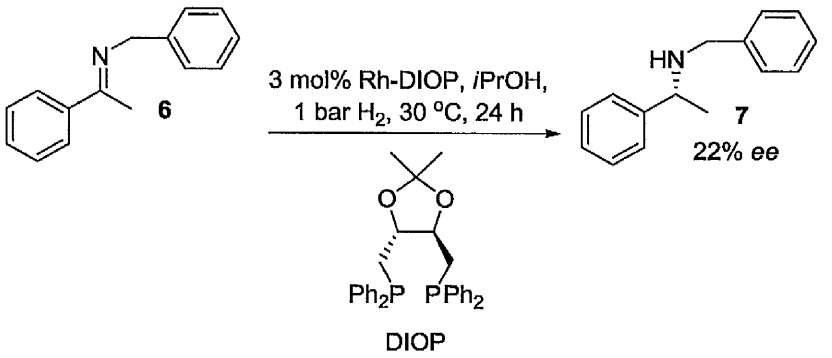
Nevertheless, the asymmetric hydrogenation of imines represents an eco-friendly, economical and effective method for the production of optically active amines. Therefore, the main work of this thesis has been focused on the review and development of highly selective metal catalysts for the synthesis of chiral amines by reduction of C=N double bonds.

## 1.3 Metal-catalysed asymmetric hydrogenation of imines

Although catalytically highly enantioselective hydrogenation of imines is still considered a challenging endeavour, the recent literature presents a wide variety of transition metal complexes for asymmetric imine hydrogenation,[16,18,20-23] where iridium complexes have shown to be the best choice in terms of enantioselectivity.[22] However, there are still two main issues that need to be addressed: the improvement of the substrate scope and the use of cheap, non-toxic metals for the metal catalysts.

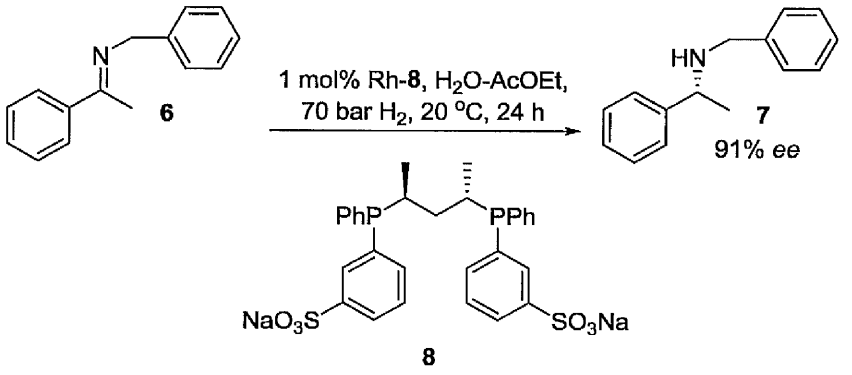
### 1.3.1 Chiral rhodium catalysts

The first example of enantioselective imine hydrogenation was reported by Scorrano in 1975.[24] A Rh-DIOP complex [DIOP: 2,2-Dimethyl-4,5-(diphenylphosphino)dimethyl)dioxolane)] was able to reduce alkenes, ketones and imines under comparable conditions. However, for imines only one substrate was shown and the enantioselectivity was very low (22% *ee*) (Scheme 1.5).




**Scheme 1.5**: First enantioselective imine hydrogenation.

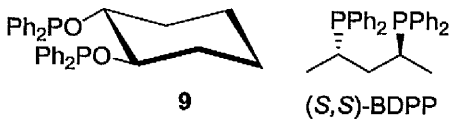
This low selectivity was not surpassed until the early 1990s, when Bakos reported a water-soluble rhodium catalyst.[25] The reaction takes place in a $H_2O$-AcOEt two-phase solvent system, with 1 mol% catalyst loading, 70 bar $H_2$ at 20 °C and an excellent 96% *ee* was reported, although only a single example was presented (Scheme 1.6).




**Scheme 1.6**: Water-soluble catalyst for imine hydrogenation.

Osborn showed an enhancement of the enantioselectivity in the presence of reverse micelles formed by AOT (AOT: sodium bis(2-ethylhexyl) sulfosuccinate) for asymmetric hydrogenation of imine **6** with the [Rh((*S,S*)-

BDPP)(NBD)]$ClO_4$ catalyst (NBD: norbornadiene) (Figure 1.2).[26] It is well-known that the use of an organized medium can have pronounced effects on certain transition-metal catalysed reactions,[27] and the increase in enantioselectivity had been previously shown in other catalytic hydrogenations.[28] The reduction takes place in benzene, under 70 bar $H_2$ at 25 °C, affording an excellent enantioselectivity (89% *ee*).

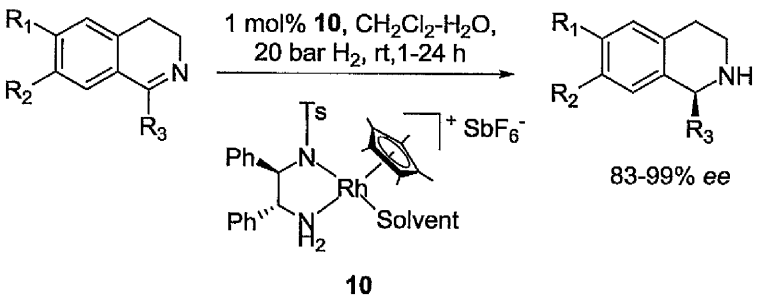



**9** (*S,S*)-BDPP

**Figure 1.2:** Ligands applied for the Rh-catalysed hydrogenation of **6.**

Börner and co-workers reported the study of a range of diphosphine and diphosphinite ligands for Rh-catalysed hydrogenation of **6**.[29] An initial screening with achiral diphosphine ligands showed that seven-membered Rh(I) chelate was the most effective, diarylphosphines were superior to dialkyl phosphines, and the addition of TsOH had a positive effect on the rate of the reaction. Upon moving to asymmetric hydrogenation, they continued their studies based on these initial results. Neutral precatalysts had better activity than the analogue cationic complexes. For the range of diphosphine ligands tested, very low enantioselectivity were reported (up to 27% *ee*). Surprisingly, rhodium complexes of chiral diphosphinites showed an excellent reactivity and good enantioselectivity, with cationic species being more effective. The best result was obtained with [Rh(**9**)COD]$BF_4$ (COD: 1,5-cyclooctadiene) (Figure 1.2).

Our group reported the asymmetric hydrogenation of 3,4-dihydroisoquinolines and 3,4-dihydro-6,7-dimethoxyisoquinolines with a cationic Rh-TsDPEN catalyst. Excellent yields and enantioselectivities were shown under 20 bar $H_2$ and 20 °C in $CH_2Cl_2$-$H_2O$ (Scheme 1.7).[30] The key to the success of **10** lies in its bulky counter-ion, $SbF_6^-$. Smaller and coordinating anions exert a dramatically inhibiting effect on the catalysis. Thus, chloride complexes lead to a much lower activity; This is probably due to unfavoured anion dissociation from the Rh(III) catalyst, which retards $H_2$ coordination. To our knowledge, this is the most effective rhodium catalyst for asymmetric hydrogenation of cyclic imines to date.

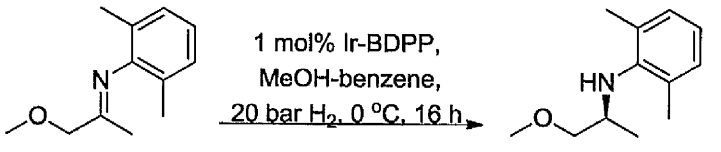



**Scheme 1.7**: Rh-TsDPEN for asymmetric reduction of cyclic imines.

### 1.3.2 Chiral iridium catalysts

The first example of enantioselective iridium-catalysed imine hydrogenation was reported by Spindler and co-workers in 1990.[31] They tested a series of diphosphine ligands with $[Ir(COD)Cl]_2$, forming the catalyst *in situ*. The best results were obtained when *(S,S)*-BDPP was used as the ligand, where 84% *ee* was obtained for the reduction of imine **11**, at 1 mol% catalyst loading, 20 bar $H_2$ and 0 °C (Scheme 1.8). There is a strong halogen effect, as addition

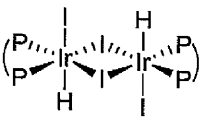
of 2 eq of iodide lead to an increase of both activity and enantioselectivity. The same would be observed for some other catalysts in the following years.[32-33] A bulky *N*-aryl group was required in order to obtain good enantioselectivity, probably due to restricted movement of the imino group.




**11** 84% *ee*

**Scheme 1.8**: First example of Ir-catalysed asymmetric imine hydrogenation.

Simultaneously and independently, Osborn and co-workers reported the discovery of a series of iridium(III)-diphosphine-monohydrido complexes **12** (Figure 1.3) and application to imine hydrogenation, DIOP and BDPP being superior over other diphosphine ligands.[34] Although lower catalyst loadings were used compared to Spindler's work (0.2-0.05 mol%), the enantioselectivities were also lower, in the range of 22-63% *ee* for hydrogenation of **11**.

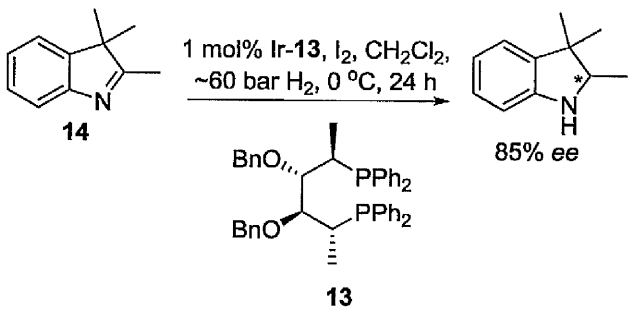



**12**

**Figure 1.3**: Iridium-diphosphine catalyst developed by Osborn.

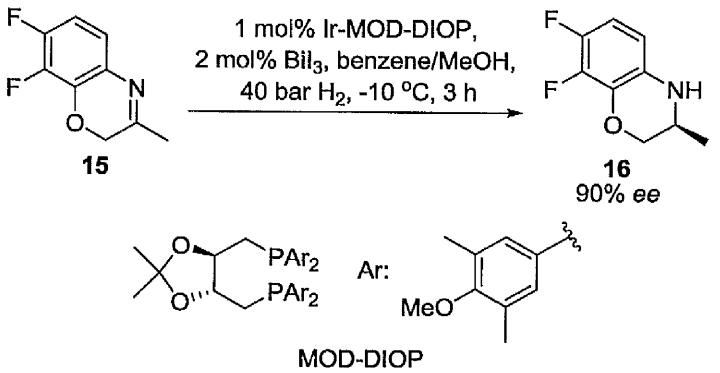
Due to these initial studies with DIOP for Ir-catalysed imine hydrogenation, other groups investigated derivatives of DIOP for the same

reduction. Zhang and co-workers extended this ligand family to ligand **13** that possesses an acyclic backbone.[33] This ligand was applied for Ir-catalysed hydrogenation of cyclic imine **14** (Scheme 1.9). With 1 mol% catalyst and 10 mol% $I_2$ as an additive, 85% *ee* was obtained at 0 °C in $CH_2Cl_2$ under ~60 bar $H_2$. Under the same conditions, only 29% *ee* was obtained with the simple DIOP.



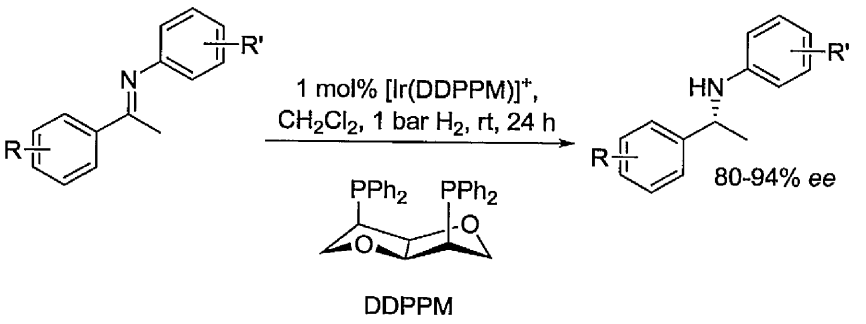

**Scheme 1.9**: Modified DIOP for asymmetric imine hydrogenation.

A modified DIOP ligand was also applied by Kanai for the synthesis of a key intermediate **16** for the antibacterial agent levofloxacin.[35] He reported the asymmetric hydrogenation of **15** by 1 mol% an Ir-MOD-DIOP catalyst at -10 °C under 40 bar $H_2$ in benzene/MeOH in the presence of 2 mol% $BiI_3$ (Scheme 1.10).[36]




**Scheme 1.10**: Synthesis of key intermediate for levofloxacin.

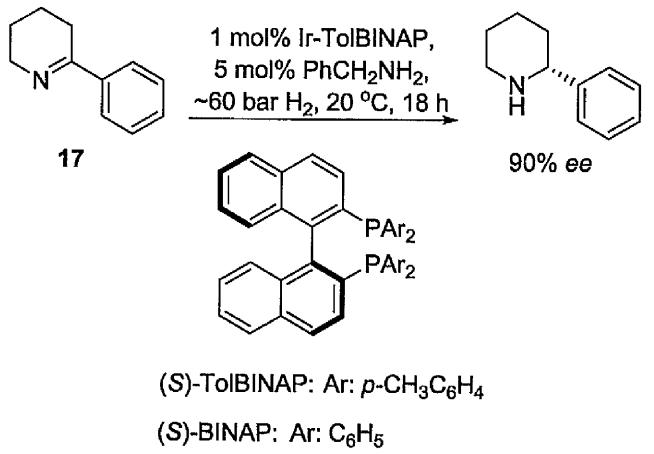
A wide range of chiral 1,4-diphosphine ligands have been applied for rhodium and iridium-catalysed imine hydrogenation (*vide supra*), although the selectivity is significantly variable. To date, the most effective 1,4 diphosphine is most certainly DDPPM.[37] A range of *N*-aryl acyclic imines were hydrogenated with excellent enantioselectivities with 1 mol% of catalyst, at ambient pressure and room temperature (Scheme 1.11). Interestingly, the increase of hydrogen pressure had a negative effect on both the activity and selectivity, probably due to the formation of inactive iridium(III) hydride clusters. This type of complex is ineffective for *N*-benzyl acyclic imines and cyclic imines.




**Scheme 1.11**: Ir-DDPPM catalyst for asymmetric acyclic imine hydrogenation.

BINAP and its derivatives also showed good performance for Ir-catalysed hydrogenation of imines. Tani found the iridium(I)-TolBINAP catalytic system to be effective for the hydrogenation of acyclic imine **6** and cyclic imine **17** (Scheme 1.12).[38] Good enantioselectivities were reported (68 and 90% *ee*, respectively) at 1 mol% catalyst, 60 bar $H_2$ and 20 °C in MeOH. Interestingly, addition of 5 mol% of a protic amine, such as benzylamine, increased both the catalytic activity and the enantioselectivity.[39] As a result, the catalytic system

without the protic amine was much less effective, with enantioselectivity no higher than 23%.




**Scheme 1.12**: Asymmetric hydrogenation of **17** with Ir-TolBINAP catalyst.

Morimoto also applied an iridium(I)-BINAP system (Scheme 1.12) for the asymmetric hydrogenation of dihydroisoquinoline **18**, a key step towards the synthesis of alkaloid *(S)*-calycotomine (Figure 1.4).[40] The reaction was carried out in a MeOH/toluene mixed solvent, at 0.5 mol% catalyst loading in the presence of 1 mol% phthalimide under 100 bar $H_2$ and 20 °C; good yield and enantioselectivity were reported.

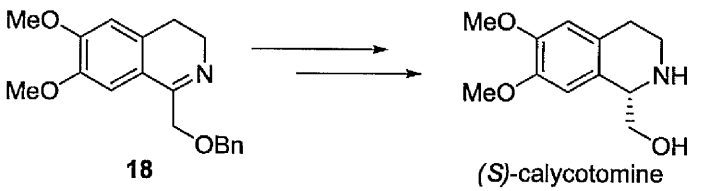
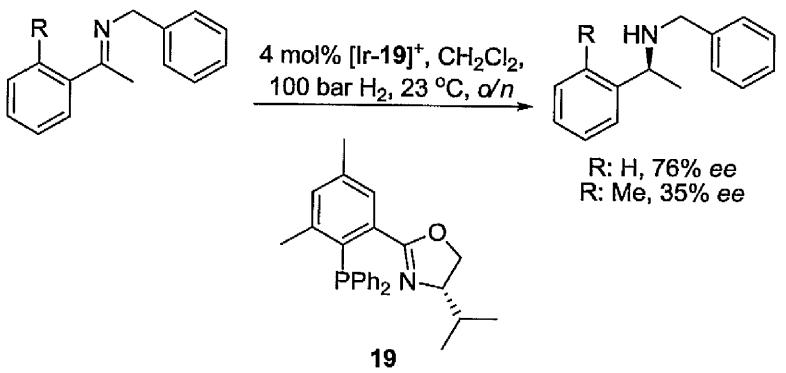



**Figure 1.4:** Imine **18** as key intermediate for alkaloid *(S)*-calycotomine.

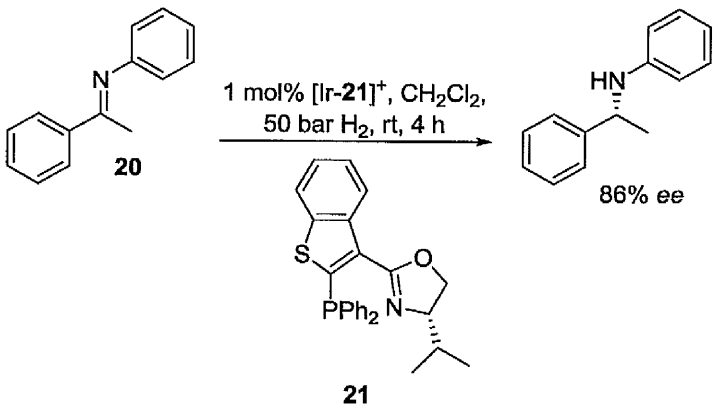
Later in the last decade, Pfaltz and co-workers reported the enantioselective imine hydrogenation with cationic iridium-phosphino oxazoline complexes at 4 mol% catalyst, 100 bar $H_2$ and 23 °C.[41] Good activities and enantioselectivities were obtained for derivatives of *N*-benzyl and *N*-aryl phenyl methyl imines. As observed with other catalysts where enantioselectivity was controlled by steric effects in the imine, *ortho*-substituted *N*-benzyl imines lead to lower enantioselectivities (from 76 to 35% *ee*). Dialkyl and cyclic imines show a significant decrease in reactivity and enantioselectivity or are just unreactive (Scheme 1.13).




**Scheme 1.13:** Asymmetric hydrogenation of imines with cationic Ir-phosphine oxazoline catalyst.

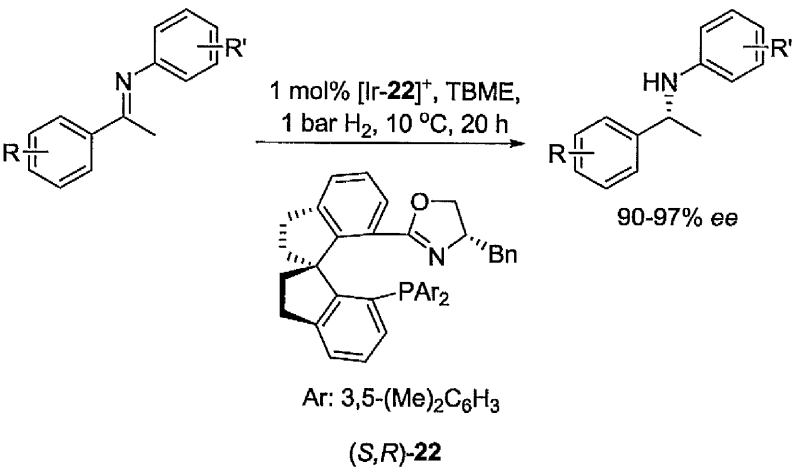
Phosphine oxazolines (PHOX) possess a modular structure that allows extensive variation of the structure in the backbone, oxazoline and phosphorus substituents. For this reason, several groups have studied different ligands from this PHOX family and applied them for Ir-catalysed imine hydrogenation in order to enhance the application range of this transformation. For example, Cozzi prepared some PHOX ligands with heterocyclic frameworks

(HetPHOX), which provides higher stability to the ligands. A series of cationic Ir-HetPHOX complexes were formed and applied to hydrogenation of an unfunctionalised olefin and imine **20**.[42] For the latter, complete reaction and 86% *ee* were obtained after 4 hours when ligand **21** was used (Scheme 1.14), with 1 mol% catalyst under 50 bar $H_2$ and room temperature.



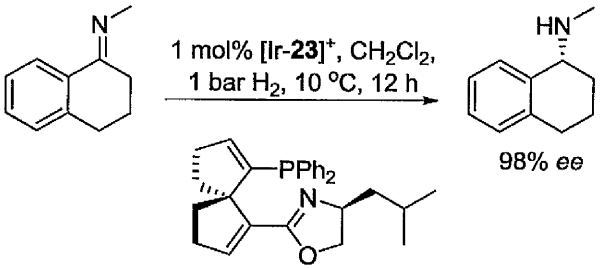

**Scheme 1.14**: P,N-ligand for asymmetric imine hydrogenation.

Zhou reported the synthesis of PHOX ligands bearing a spirobiindane backbone (SIPHOX), which is extremely rigid and bulky; then the cationic iridium complex was formed and applied in asymmetric hydrogenation of *N*-aryl acyclic imines.[43] There was a clear match/mismatch effect between the chirality in the spirobiindane backbone and the oxazoline ring, the best combination being *(S,R)* configuration (Scheme 1.15). Excellent yields and enantioselectivities were reported at ambient hydrogen pressure and 10 °C in methyl*tert*-butyl ether (MTBE) (Scheme 1.15).




**Scheme 1.15**: Example of SIPHOX ligand for Ir-catalysed asymmetric imine hydrogenation.

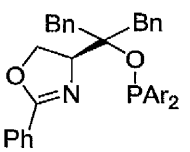
More recently, Ding and co-workers extended this family of spiro PHOX ligands by developing the corresponding spiro[4,4]-1,6-nonadiene system (SpinPHOX) **23** (Scheme 1.16), and applied them for asymmetric imine hydrogenation.[44] Forming a cationic Ir-complex, this type of catalysts surpassed Zhou's Ir-SIPHOX in terms of activity and especially scope. A wide range of substrates were hydrogenated with excellent yields and enantioselectivities, including in particular the more challenging *N*-alkyl imines. The reduction undergoes at ambient hydrogen pressure, 10 °C with 1 mol% catalyst and complete conversion is achieved after only 8-12 hours (Scheme 1.16).




**23**

**Scheme 1.16**: Example of *N*-alkyl imine hydrogenation with Ir-SpinPHOX.

In addition to the PHOX type ligands, several groups developed other P,N ligands for iridium-catalysed hydrogenation of imines. Pfaltz and co-workers synthesised a series of phosphinite-oxazoline ligands derived from serine[45] and threonine[46] and applied them to iridium-catalysed unfunctionalised olefin hydrogenation. For those ligands derived from threonine, the hydrogenation of *N*-aryl imine **20** was briefly investigated.[46] The Ir-**24** catalyst shows good activity, and the reaction goes to completion after 4 hours with 1 mol% catalyst under 50 bar $H_2$ at room temperature; but good enantioselectivity is only reported with ligand **24** (80% *ee*) (Figure 1.5).




Ar: *o*-$MeC_6H_4$

**24**

**Figure 1.5**: Phosphinite-oxazoline ligand derived from threonine.

In the last decade, Pfaltz and co-workers synthesised a wide range of novel P,N ligands, applying them to hydrogenation of olefins.[47] Very recently, they reinvestigated the asymmetric imine hydrogenation by applying the cationic Ir-

P,N ligand complexes developed in their laboratory in the previous years. Three different chiral oxazoline-based P,N ligands, including some PHOX ligands, were identified as highly efficient for the enantioselective hydrogenation of *N*-aryl imines from arylalkylketones (Figure 1.6).[48] Only 0.5 mol% catalyst is required to achieve completion after 6-8 hours, at a pressure of 5 bar $H_2$ at -20 °C. Enantioselectivities in the range of 74-96% *ee* were reported.

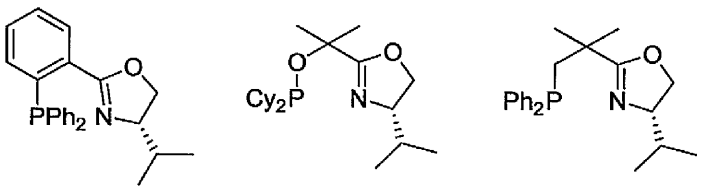
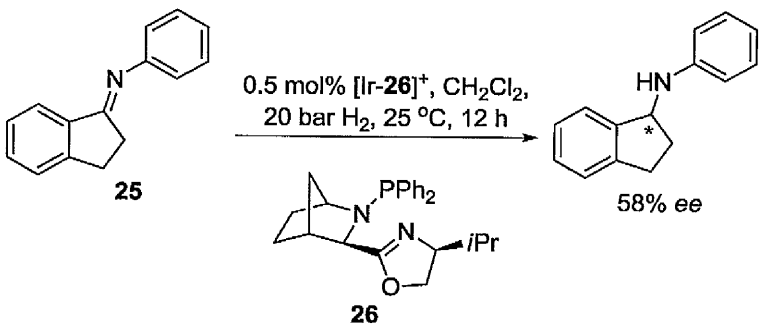



**Figure 1.6**: Three most efficient Pfaltz P,N-ligands for asymmetric imine hydrogenation.

Blanc reported the application of aminophosphine-oxazoline ligands for Ir-catalysed enantioselective imine hydrogenation.[49] These ligands are prepared from two optically active aminoacids; one provides the chiral oxazoline unit while the other one the chiral aminophosphine moiety. The cationic iridium complexes were then prepared and applied for imine hydrogenation of *N*-phenyl and *N*-benzyl phenylmethyl imines. At the same time, Andersson reported a different class of chiral aminophosphine-oxazoline ligands for the Ir-catalysed asymmetric hydrogenation of *N*-arylimines.[50] At 0.5 mol% catalyst loading, 20 bar $H_2$ and room temperature, good yields and excellent enantioselectivities were reported (83-90%). Low pressure (5 bar $H_2$) and lower catalyst loading (0.05 mol%) can be applied without effect on the

enantioselectivity, albeit with low activity. They then extended this work to the reduction of bulkier imines, such as imine **25**, derived from 1-indanone, where only moderate *ee*'s were obtained (Scheme 1.17).[51]




**Scheme 1.17**: Asymmetric hydrogenation of bulky imine **25**.

Diphosphine ligands with a ferrocene backbone have been highly efficient for asymmetric imine hydrogenation. Blaser applied the ligand XYLIPHOS (Figure 1.7) for the synthesis of herbicide *(S)*-metolachlor by reductive amination or industrially by imine hydrogenation (*vide infra*).[52] The fact that the two phosphine groups in this class of ferrocenyl diphosphine ligands can be introduced sequentially provides a great advantage in terms of tunability of the ligand. in this regard, Blaser and co-workers studied the relationship between structure and selectivity for the Ir-catalysed enantioselective hydrogenation of *N*-aryl imines.[53] Although high enantioselectivities were obtained for various imines, every substrate required an optimal combination of R and R' groups, and therefore, the catalyst lacks generality, requiring optimisation for each substrate. Furthermore, Reetz reported moderate enantioselectivity (79% *ee*)

for the Ir-catalysed hydrogenation of **14** with a ferrocene-backbone diphosphine ligand **27**, containing only planar chirality (Figure 1.7).[54]

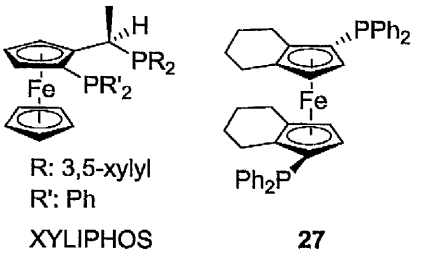
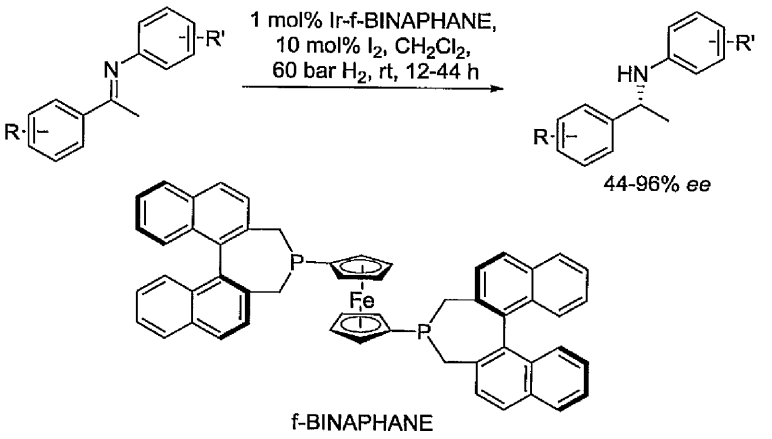


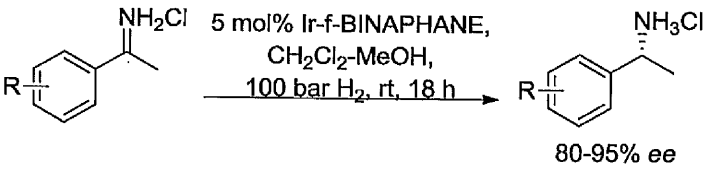

**Figure 1.7**: Ferrocene-based diphosphine ligands applied for Ir-catalysed imine hydrogenation.

Zhang reported the first highly enantioselective imine hydrogenation using an Ir-f-BINAPHANE complex. At 60 bar $H_2$ and room temperature, a series of imines derived from aromatic ketones were hydrogenated with excellent enantioselectivities (Scheme 1.18).[32] However, the catalyst is not effective for the hydrogenation of imines from aliphatic ketones, with low conversions and enantioselectivities reported. Best results were obtained when weaker coordinating solvents were used, such as $CH_2Cl_2$. The enantioselectivity improves when sterically hindered anilines were used, as best *ee*'s were obtained with 2,6-dimethylaniline. The effect of addition of $I_2$ is not clear.[55] When imines from less bulky anilines were used, the addition of $I_2$ had a positive effect on the enantioselectivity. However, when the imine came from the bulky 2,6-dimethylaniline, both the activity and enantioselectivity dropped considerably in the presence of $I_2$ (from 64% and 98% to 8% and 69%, respectively). They then applied this catalyst for the reductive amination of ketones (*vide infra*).



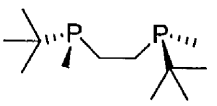

**Scheme 1.18**: Asymmetric imine hydrogenation with Ir-f-BINAPHANE catalyst.

As Ir-f-BINAPHANE proved to be an excellent catalyst for imine hydrogenation, Zhang *et al.* then applied the complex to the first example of enantioselective hydrogenation of unprotected N-H imines, leading to chiral primary amines without the need of protection/deprotection (Scheme 1.19).[56] The hydrogenation takes place under high pressure of 100 bar $H_2$, at room temperature in a solvent combination of $CH_2Cl_2$ and MeOH. Interestingly, the substitution of chloride by non-coordinating counterions in the imine had a negative effect on the enantioselectivity. Excellent enantioselectivities were reported for aryl-methyl imines, while hydrogenation of alkyl-methyl imines led to poor *ee*'s.




**Scheme 1.19**: Enantioselective hydrogenation of unprotected N-H imines.

Some P-chiral diphosphine ligands have also shown to be effective for hydrogenation of imines with iridium catalyst. Imamoto reported the synthesis of (*S,S*)-t-Bu-BisP* ligand **28** (Figure 1.8) and its application for Ir-catalysed hydrogenation of acyclic *N*-aryl imines.[57] The reaction proceeds under mild conditions at ambient hydrogen pressure and temperature and only 0.5 mol% catalyst loading, affording excellent enantioselectivities (up to 99% *ee*), which surpassed other diphosphine ligands in iridium complexes, such as BINAP or P,N-ligands such as Ph-PHOX and *i*Pr-PHOX. Better selectivity is obtained when electron-deficient imines are used as substrates. Unfortunately, this catalyst shows no effectiveness for the hydrogenation of *N*-aryl dialkyl imines.



**28**

**Figure 1.8:** P-chiral diphosphine ligand applied to Ir-catalysed hydrogenation of imines.

More recently, Zhang and co-workers reported highly efficient asymmetric hydrogenation of acyclic *N*-arylimines catalysed by the Ir-DuanPHOS complex (Figure 1.9).[58] Excellent enantioselectivities were reported for a series of substrates under 50 bar $H_2$ and room temperature at 0.5 mol% catalyst loading. Interestingly, much milder conditions can be used without detriment of the selectivity. Thus, the imine can be completely hydrogenated at 5 bar $H_2$ with only 0.01 mol% catalyst after 18 hours. This is one of the best turnover number (TON) (10,000) for iridium-catalysed imine hydrogenation.

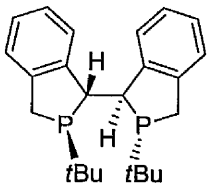
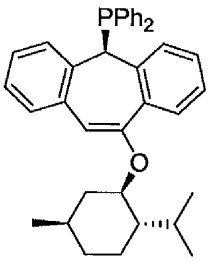



**Figure 1.9**: Ligand DuanPHOS.

The phosphine-olefin ligand **29** (Figure 1.10) has been applied for the iridium-catalysed hydrogenation of imine **20**, providing good enantioselectivity (86% *ee*).[59] It was the first example of a chiral olefin used as directing ligand for enantioselective hydrogenation.




(*R,R*)-**29**

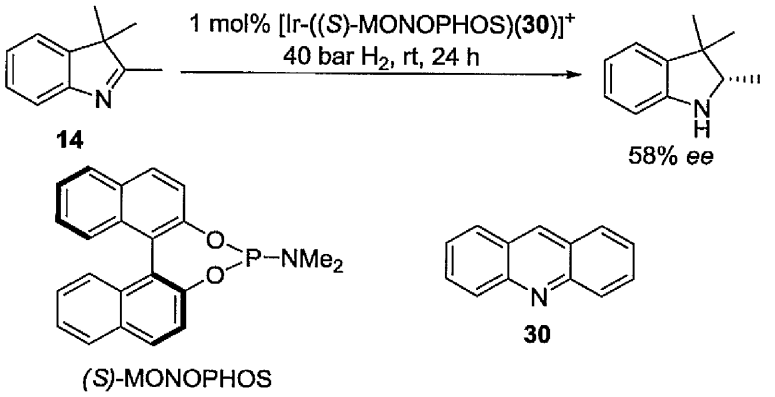
**Figure 1.10**: Phosphine olefin ligand.

Leaving the world of phosphine-containing ligands for Ir-catalysed imine hydrogenation, other ligands have also shown high selectivity. Feringa studied the application of chiral secondary phosphine oxides (SPOs) as monodentate ligands.[60] These phosphine oxides exist in tautomeric equilibrium between the pentavalent (phosphine oxide) and the trivalent (phosphinite) forms and it is the latter that coordinates to the transition metal centre (Figure 1.11). The iridium catalyst reduces *N*-benzyl imines with good to high enantioselectivity but only racemic mixture is obtained in the reduction of **20**. The reaction takes

place at high catalyst loading of 5 mol% under 25 bar $H_2$ and room temperature. This is the first example of the application of SPOs as ligands in asymmetric catalysis.

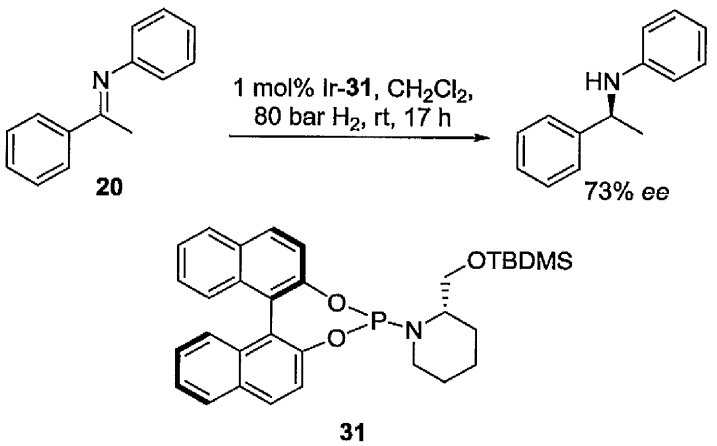

**Figure 1.11**: Tautomeric equilibrium of SPOs.

Subsequently, Faller reported an iridium catalyst containing a chiral monodentate phosphoramidite in combination with *N*-donor ligands for asymmetric hydrogenation of cyclic imine **14**.[61] The best result was obtained with the combination of (*S*)-MONOPHOS and an *N*-donor ligand **30**; but only a moderate enantioselectivity of 58% was obtained (Scheme 1.20). The reduction proceeded with 1 mol% catalyst under 40 bar $H_2$ at room temperature and solvent-free conditions.




**Scheme 1.20**: Combination of phosphoradimite with *N*-donor ligand for Ir-catalysed imine hydrogenation.

Simultaneously and independently, Murai reported the synthesis of a new class of phosphoradimites.[62] The application to the hydrogenation of imines with an iridium complex led to a more successful result, with enantioselectivity up to 73% for acyclic imine **20**, which historically gave lower selectivities than cyclic imines, due to the easy interconversion of *E*- and *Z*-isomers of acyclic imines in solution (*vide supra*) (Scheme 1.21). The catalyst is formed *in situ* and the reaction takes place under a pressure of 80 bar $H_2$ and room temperature in $CH_2Cl_2$.




**Scheme 1.21**: Hydrogenation of acyclic imine with Ir-phosphoradimite complex.

Related chiral phosphoramidites **32** (Figure 1.12) were also applied for Ir-catalysed hydrogenation of N-H benzophenone imines, leading to protection-free chiral diarylmethylamines.[63] The use of chloride as counterion proved to be superior to non-coordinating counterions such as $BF_4^-$. This was also observed previously with the Ir-f-BINAPHANE system (*vide supra*).[56] The presence of bulky groups at the *ortho*-position of the aromatic ring was

required to obtain high enantioselectivity. As a comparison, *o*-trifluomethyl, *o*-methyl and *p*-methyl substituents led to 98, 82 and 31% *ee*, respectively (Figure 1.12).

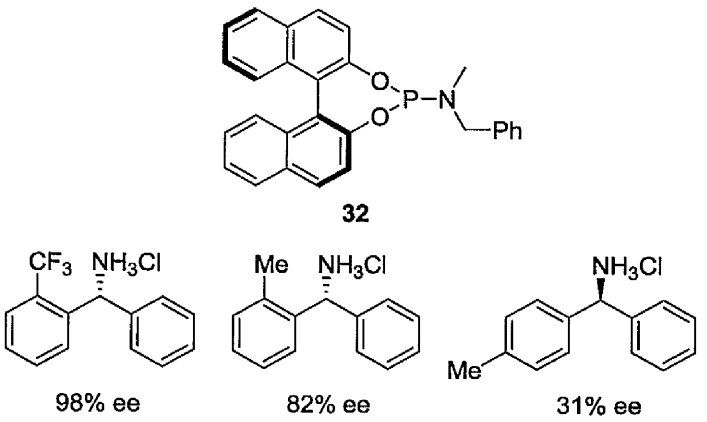
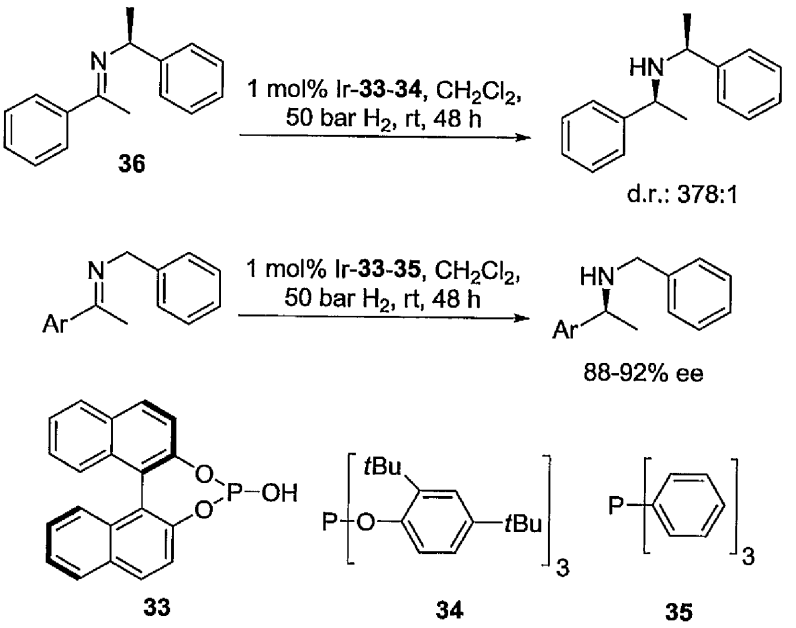



**Figure 1.12:** Diarylmethylamines synthesised with Ir-**32** catalyst.

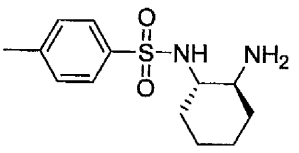
In addition to phosphoramidites, phosphites with the binol skeleton have also been applied in iridium hydrogenation. Reetz and co-workers reported heterocombinations of chiral phosphite **32** with different monophosphine ligands, showing a positive effect on the selectivity compared to the corresponding chiral homocombination.[64] They first studied the combination of phosphite **33** and phosphonites with monophosphine ligands for the diastereoselective hydrogenation of imine **36**. In general, the optimal combination is composed of a relatively small monophosphine with the bulky phosphite **33**. For hydrogenation of **36**, the best result was obtained when **33** and **34** were combined, obtaining a diastereoselectivity ratio of 378:1 (Scheme 1.22). They then moved on to the enantioselective hydrogenation of *N*-benzyl imines, where the combinations were restricted to those ligands that had previously displayed the best enhancement of diastereoselectivity.

Enantioselectivities up to 92% *ee* were reported. In terms of selectivity, this is one of the best results obtained for *N*-benzylamines to date, although the reaction is carried out at high pressure and requires long reaction times.




**Scheme 1.22**: Hetero-combination of ligands applied to hydrogenation of imines.

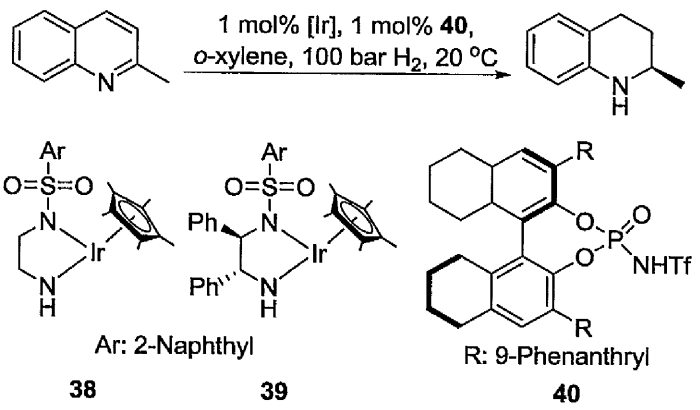
In 2009, Ikariya reported the enantioselective hydrogenation of *N*-benzyl imines with a cationic IrCp* (Cp*: pentamethyl cyclopentadienyl) ligated with the chiral sulfonylated diamine ligand **37** (Figure 1.13).[65] Enantioselectivities up to 78% *ee* were obtained under 20 bar $H_2$ at 30 °C. However, only racemic mixture is obtained when **20** is hydrogenated. Similarly to the hydrogenation of cyclic imines with cationic Rh-TsDPEN reported by our group (*vide supra*),[30] Ikariya observed positive effects of the silver salts, $AgSbF_6$ being the best in terms of activity and selectivity.



**37**

**Figure 1.13**: Chiral *N*-tosylated diamine ligand for iridium catalysis.

More recently, Rueping reported the combination of an achiral IrCp*-diamine complex with a chiral *N*-trifylphosphoramide for the asymmetric hydrogenation of quinolines.[66] The inspiration for this work came from a previous work in this group, where the combination of a chiral IrCp*-diamine with chiral Brønsted acid had a synergetic effect on the enantioselectivity for the hydrogenation of imines and reductive amination of ketones. In unpublished work, our group had explored similar combinations, achieving 73% *ee*, in hydrogenation of *p*-methoxy-*N*-(1-phenylethylidene)aniline.[67] This work is explained in more detail in the following chapter. Rueping and co-workers envisioned that the chiral Brønsted acid **40** could induce chirality on the metal complex **38** (Scheme 1.23). Unfortunately, low enantioselectivity was observed for the hydrogenation of quinolines (up to 38% *ee*). More successful was the combination of the chiral **39** with **40**. And interestingly, **40** kinetically discriminates **39**, with **40**-(*R,R*)-**39** being more active and selective (Scheme 1.23).




| [Ir] | Time (h) | Conv. (%) | *ee* (%) |
|---|---|---|---|
| **38** | 60 | 40 | 32 |
| *rac*-**39** | 24 | > 95 | 82 |
| (*S,S*)-**39** | 40 | 75 | - 68 |
| (*R,R*)-**39** | 24 | > 95 | 88 |

**Scheme 1.23**: Effect of the metal complex for the cooperative catalysis for the asymmetric hydrogenation of quinolines.

### 1.3.3 Chiral ruthenium catalysts

Morris and co-workers introduced the Noyori type ruthenium diphosphine/diamine complexes (Figure 1.14) for the asymmetric hydrogenation of imines. Both *N*-aryl and *N*-alkyl acyclic imines were hydrogenated under mild conditions (3 bar $H_2$ and 20 °C) at 0.2 mol% **41** in the presence of catalytic amounts of KO*i*Pr, resulting in moderate to good enantioselectivities (up to 71% *ee*).[68] The presence of the base is essential for the effectiveness of the catalyst, suggesting that the true catalyst might be formed after the loss of HCl, possibly a dihydride species derived from **41** (Figure 1.14).

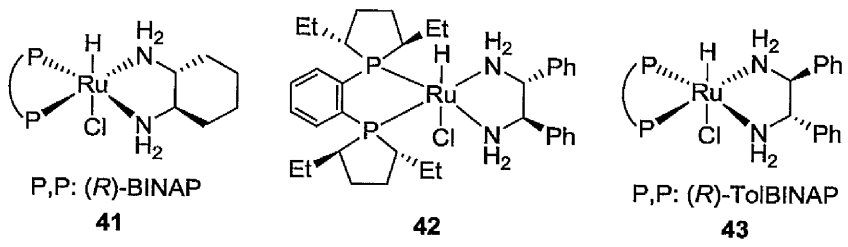



**Figure 1.14:** Noyori's type catalyst applied for asymmetric hydrogenation of imines.

Other groups also studied the effect of different diphosphine and diamine ligands in the Noyori type catalyst for asymmetric imine hydrogenation.[69-70] Cobley screened a wide library of diphosphine and diamine ligands for different imine substrates, unfortunately finding that every substrate requires an extensive screening and it is difficult to predict the best combination.[69] For *N*-aryl imines, the complex **42**, containing ligands (*R,R*)-Et-DuPHOS and (*R,R*)-DPEN, (Figure 1.14) gave the best selectivity of 91% *ee*, at 1 mol% catalyst, 65 °C under 15 bar $H_2$ in the presence of 1 eq of base in *i*PrOH. In the case of *N*-benzyl imine **6**, the best combination of ligands was found to be (*S*)-TolBINAP and (*S,S*)-DPEN, forming complex **43** (Figure 1.14). For this substrate, only 5 mol% of base is used, as an increase of the amount of base favours the equilibrium mixture between **6** and its aldimine tautomer, which could be hydrogenated to give a racemic product (Figure 1.15).

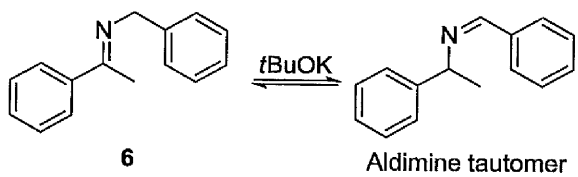
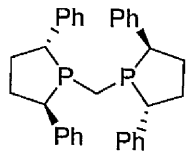



**Figure 1.15**: Equilibrium of **4** and its aldimine tautomer.

Jackson developed a new diphosphine ligand (*R,R*)-Ph-BPM **44** (Figure 1.16) and then applied the complex [Ru((*R,R*)-Ph-BPM)((*S,S*)-DPEN)$Cl_2$] to enatioselective imine hydrogenation.[70] Although only 3 substrates are reported, the catalyst is effective for *N*-aryl and *N*-benzyl acyclic imines and a cyclic imine, displaying good selectivities (71-89% *ee*). There is a clear match/mismatch between the phosphine and the amine, as the opposite configuration on the amine showed inferior selectivity.

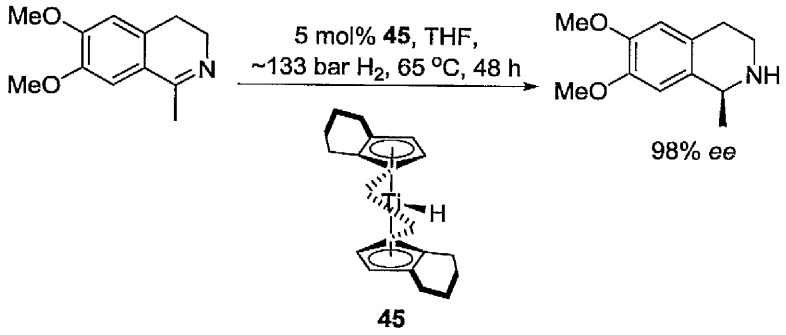



**44**

**Figure 1.16**: (*R,R*)-Ph-BPM ligand.

### 1.3.4 Other chiral metal catalysts

In 1992, Buchwald applied the ansa-titanocene system **45** developed by Brintzinger[71] to the first example of asymmetric hydrogenation of imines (Scheme 1.24).[72] The reaction occurs at ~130 bar $H_2$, 65 °C with 5 mol% catalyst loading. While the reduction of cyclic imines takes place with excellent enantioselectivity, only moderate to good enantioselectivities (up to 76% *ee*) are obtained for the reduction of acyclic *N*-benzyl imines.




**Scheme 1.24**: Example of hydrogenation of cyclic imine by titanocene catalyst.

Brintzinger developed a different class of chiral ansa-titanocene catalyst **46** (Figure 1.17), and also applied them for enantioselective imine hydrogenation.[73] Although similar selectivity for both cyclic and acyclic imines is obtained to that reported by Buchwald, the catalyst activity is much higher, as only 0.1 mol% of titanium complex is required to complete the reaction in 12 hours, at 150 bar $H_2$ and 80 °C.

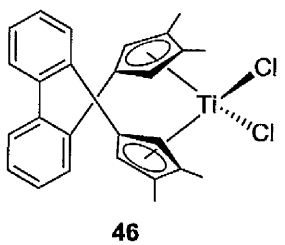
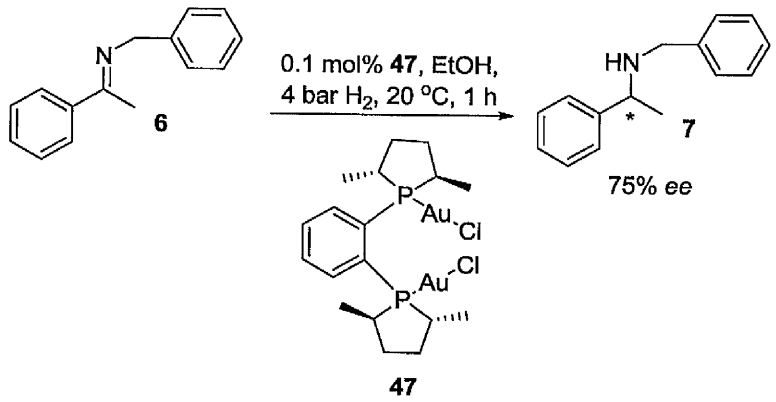



**Figure 1.17**: Chiral biphenyl-bridged titanocene complex developed by Brintzinger.

Corma and co-workers reported the first example of gold complex as a hydrogenation catalyst for the reduction of alkenes and imines.[74] Only recently have gold complexes been studied in catalysis, which had always been thought as being chemically inert. The hydrogenation of **6** takes place with a dimeric

gold(I) complex **47** with (*R,R*)-Me-DuPHOS ligand, at only 0.2 mol% catalyst loading, 20 °C under a low pressure of 4 bar $H_2$ (Scheme 1.25).




**Scheme 1.25**: Gold-catalysed asymmetric hydrogenation of **6**.

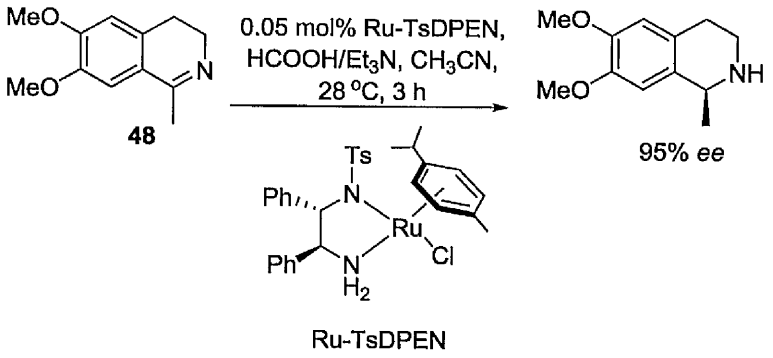
## 1.4 Metal-catalysed asymmetric transfer hydrogenation of imines

In a transfer hydrogenation (TH) reaction, the hydrogen source is other than hydrogen gas.[75] The most commonly used hydrogen sources are *i*PrOH and azeotropic mixture of formic acid/triethylamine. Metal-catalysed asymmetric transfer hydrogenation (ATH) of ketones has been widely reported in the literature, with an impressive number of successful examples for the synthesis of chiral secondary alcohols.[11,76-81] However, ATH of imines has been less developed, despite the synthetic importance of chiral amines.[23,82]

### 1.4.1 Precious metal-catalysed ATH of imines

The first example of ATH of imines was reported by Noyori in 1996. Excellent enantioselectivities were reported for ATH of cyclic imines with 0.05 mol% of Ru-TsDPEN catalyst, using a mixture of formic acid/triethylamine as

hydrogen source under mild conditions (Scheme 1.26).[83] The reduction of acyclic imines is somewhat less stereoselective. For example, ATH of **6** led to only 77% *ee*. The presence of triethylamine is essential; in the absence of triethylamine, the Ru-TsDPEN complex catalysed the decomposition of formic acid into $H_2$ and $CO_2$.[84-85]




**Scheme 1.26**: ATH of an isoquinoline **48** with Ru-TsDPEN catalyst.

Since this discovery, this Ru-TsDPEN system has been applied for synthesis of key intermediates of important drugs,[86-89] such as neuromuscular blocker GW 0430[86] or opiate analgesic morphine[87] (Figure 1.18). Furthermore, derivatives of the Ru-TsDPEN catalyst have been developed for ATH of other cyclic imines.[90-93]

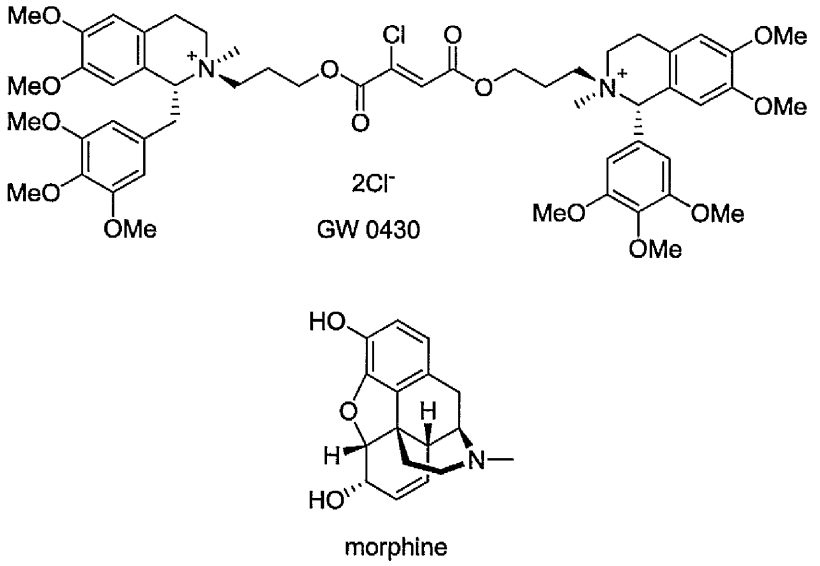



**Figure 1.18**: Structures of GW 0430 and morphine.

Deng and co-workers developed the first ATH of cyclic imines in water. They had previously reported the ATH of ketones in water,[94] and then expanded it to imines. The reaction takes place using $HCO_2Na$ as hydrogen source, under mild conditions, with 1 mol% Ru catalyst, which is formed with water-soluble ligand **49**, a derivative of Ts-DPEN (Figure 1.19), and in the presence of a surfactant, **48** could be reduced to completion after 10 hours with 95% *ee*. A variety of cyclic imines were reduced, including 3,4-dihydro-β-carbolines and *N*-sulfonylimines. Attempts at ATH of **6** led to complete decomposition of the substrate, however.

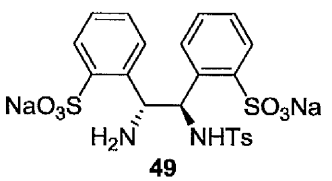
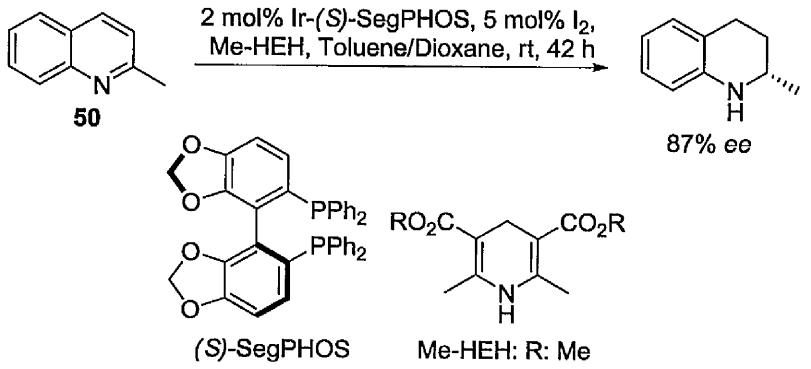


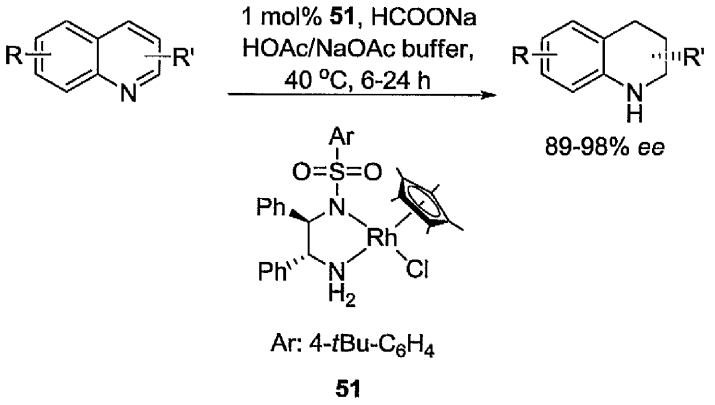

**Figure 1.19:** Water-soluble ligand **49**.

Zhou and co-workers developed the ATH of quinolines with an Ir-*(S)*-SegPHOS catalyst and Me-Hantzsch ester (Me-HEH) as hydrogen source (Scheme 1.27).[95] Although good enantioselectivities are reported (81-87% *ee*), the use of Me-HEH as the hydrogen source necessitates long reaction times (42-79 hours).




**Scheme 1.27**: ATH of quinolines with Me-HEH as hydrogen source.

The first example of ATH of quinolines in water was developed within the Xiao group.[96] Enantioselectivities in the range of 89-98% *ee* were reported for a wide range of quinolines. The conditions were optimised for **50**. The reaction takes place in water, at 40 °C with 1 mol% catalyst loading and azeotropic HCOOH/$Et_3N$ as hydrogen source (Scheme 1.28). A buffer system (HOAc/NaOAc) was required to maintain the pH of the reaction media at an optimal value of 5. It is understood that this reduction follows an ionic pathway,[97-98] where the corresponding iminium cation is the actual species reduced. Therefore a pH where **50** can be protonated is required (pKa of protonated **50** is 5.4).




**Scheme 1.28**: ATH of quinolines in water.

### 1.4.2 Fe-catalysed ATH of imines

The homogeneous catalysed asymmetric reduction of imines is dominated by Ir, Ru, Rh, and Ti complexes. However, cheap metal catalysts are more desirable from an economical and environmental point of view. In this regard, recent papers have attempted the iron-catalysed asymmetric reduction of imines, although this area is still relatively unexplored.

Morris *et al.* reported the ATH of ketones with a Fe-PNNP catalyst (Figure 1.20), using *i*PrOH as the hydrogen source in the presence of a strong base KO$^t$Bu.[99] They also reduced an aldimine, which showed much lower activity, and unfortunately catalyst **52** was almost inactive for the reduction of a ketimine.[100]

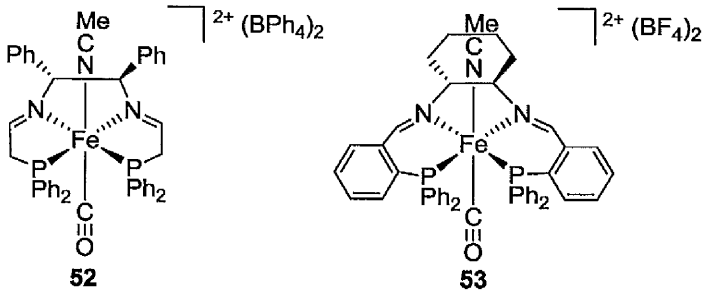
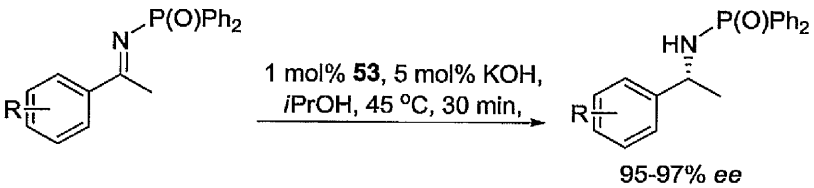



**Figure 1.20**: Fe-PNNP catalysts for ATH.

More successful are the results reported by Beller and co-workers for the ATH of *N*-(diphenylphosphinyl)ketimines.[101] Complex **53** (Figure 1.20), previously reported by Morris,[102] was proven to be the most selective for this reduction. These substrates possess the advantage of not undergoing *E/Z* isomerisation, characteristic of simple *N*-aryl imines. This catalyst shows high activity, as the reaction goes to completion after 30 minutes with 1 mol% complex, at 45 °C in the presence of a strong base KOH and *i*PrOH. Excellent enantioselectivities (95-97% *ee*) were reported (Scheme 1.29).

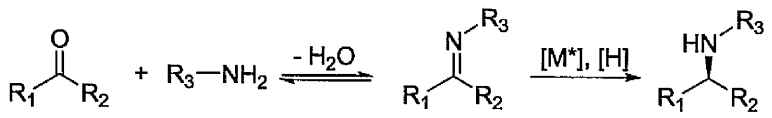



**Scheme 1.29**: ATH of *N*-(diphenylphosphinyl)ketimines.

## 1.5 Metal-catalysed asymmetric reductive amination

Direct asymmetric reductive amination (DARA) of prochiral ketones for the synthesis of α-chiral amines has been considered one of the key green chemistry research areas by the ACS GCI (Green Chemistry Institute)

Pharmaceutical Roundtable.[103] It represents a more eco-friendly pathway for the synthesis of chiral amines. This reductive amination procedure consists of a one-pot two-step reaction. Firstly, the imine is formed from the condensation of a prochiral ketone and an amine. This is followed by *in situ* asymmetric reduction of the corresponding imine (Scheme 1.30). The isolation of the imine intermediate is not required, which is historically known as a tedious and difficult process due to low stability of imines.




**Scheme 1.30**: General scheme for DARA.

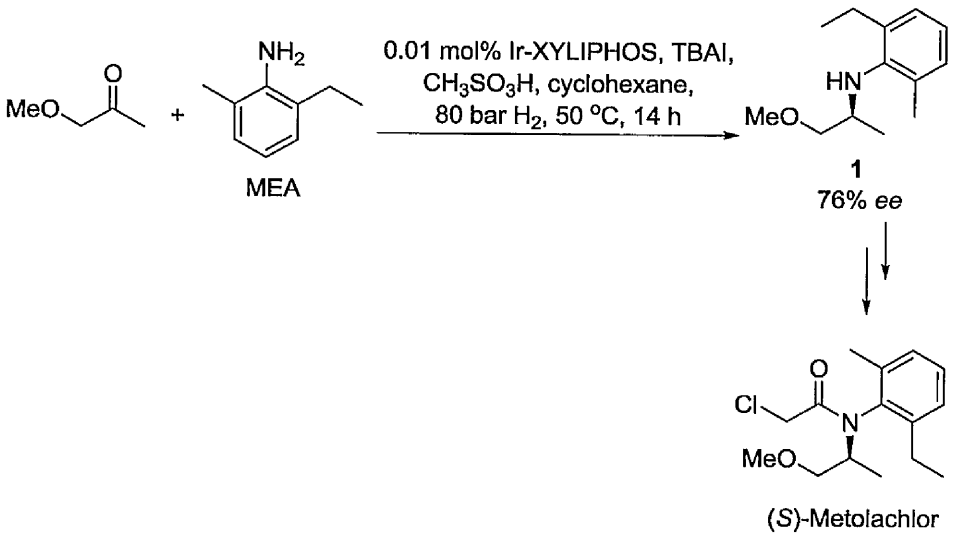
Recently, there has been a significant development in asymmetric catalytic imine reduction. However, there are still only a few examples in the literature for DARA.[104-105] Although it is considered of high importance in the pharmaceutical industry, this reaction possesses several challenges: competition reaction between ketone reduction and the imine reduction, and inhibition of the catalyst by the amine substrate or product.

### 1.5.1 Metal-catalysed DARA under hydrogenation conditions

The first enantioselective reductive amination was reported by Blaser in 1999 for the synthesis of *(S)*-metolachlor, which is the active ingredient in the herbicide Dual (Scheme 1.31).[106] The idea was to improve the optimised industrial process, where the isolated imine is hydrogenated at 80 bar $H_2$ and

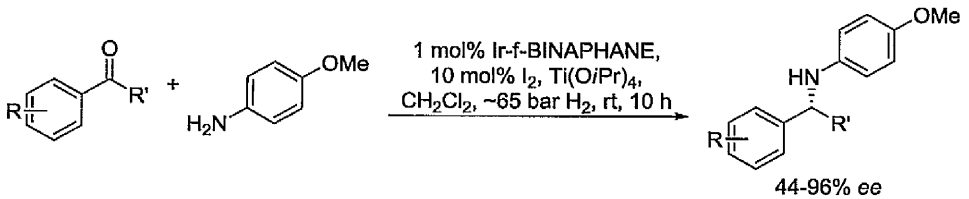
50 °C with an Ir-XYLIPHOS complex formed in situ.[52-53,107] This imine hydrogenation takes place at an excellent S/C ratio of $10^6$, with initial turnover frequency (TOF) of $1.8 \times 10^6$ $h^{-1}$, 3-4 hours reaction time and around 80% *ee*. During the study of the one-pot process, they determined that addition of a strong acid such as trifluoroacetic acid, tetra butyl ammonium iodide (TBAI) and a cosolvent was required. Cyclohexane was shown to be the best cosolvent in terms of activity and enantioselectivity, probably due to the low solubility of water and 2-methyl-5-ethylaniline (MEA) in the organic solvent, which are known to deactivate the Ir-XYLIPHOS catalyst.[31,108-109] The reaction is complete after 14 hours with a S/C ratio of 10,000 and enantioselectivity of 76-78% *ee*. Although this new process avoids isolation of the imine intermediate, the activity of the catalyst drops considerably; hence the imine hydrogenation process is still the pathway of choice from the economical point of view.

the economical point of view.



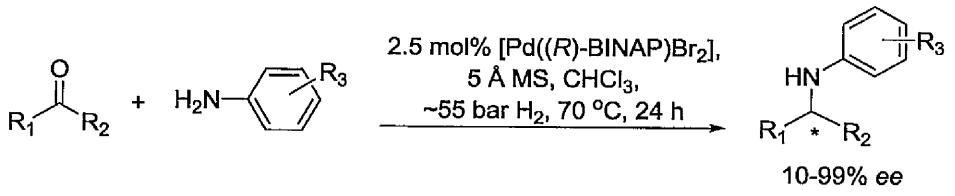

**Scheme 1.31:** Reductive amination with Ir-XYLIPHOS catalyst.

In 2003, Zhang and co-workers reported the DARA of aryl ketones with Ir-f-BINAPHANE catalyst[110] (Scheme 1.32), which they previously proved to be effective for the asymmetric hydrogenation of imines.[32] Preliminary studies concluded that the formation of the imine was the rate-limiting step. Therefore, different substances were used as additives to promote the imine formation. The presence of $Ti(O^iPr)_4$ clearly accelerates the reaction, while other additives such as 4 Å molecular sieves (MS), $MgSO_4$ or TsOH did not show any positive effect. Optimised conditions were found to be 1 mol% of the catalyst, 10 mol% $I_2$ and 1.5 eq of $Ti(O^iPr)_4$ at room temperature and ~65 bar $H_2$. Excellent enantioselectivities were obtained for a range of aryl ketones in the presence of *p*-anisidine. The enantioselectivity dropped for more sterically hindered ketones: from phenyl methyl ketone, to phenyl ethyl ketone to phenyl *n*-butyl ketone, the enantioselectivity dropped from 94 and 85 to 79% ee. The different methyl-substituted acetophenones led to a similar trend, where the enantioselectivity dropped considerably from *p*-methylacetophenone with 96% *ee*, to 89% *ee* for *m*-methylacetophenone to a low 44% *ee* for *o*-methylacetophenone. The main drawback of this catalyst is its ineffectiveness for the DARA of aliphatic ketones.




**Scheme 1.32:** DARA of ketones with Ir-f-BINAPHANE catalyst.

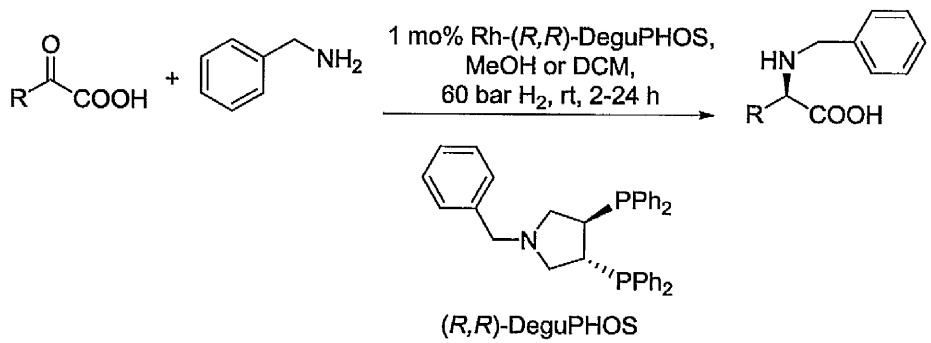
More recently, Rubio-Pérez and co-workers reported DARA of ketones with an air-stable chiral Pd-BINAP catalyst (Scheme 1.33).[111] The comparison of different diphosphine ligands showed that a larger bite angle increased the performance of the catalyst. The optimised conditions were found to be 2.5 mol% catalyst, ~55 bar $H_2$ at 70 °C in chloroform in the presence of 5 Å MS. The reaction performs well for a series of aliphatic ketones with good yields and good to excellent enantioselectivities. The presence of substituents in the aniline increases the enantioselectivity and the catalyst still performs well when substituted or sterically hindered aliphatic ketones are employed. When 2,3-butanedione is used, the catalyst proved to be chemoselective to the monoaminated product, but product is almost racemic (10% *ee*). GC-MS experiments showed the catalyst is selective for imine reduction over the ketone, as no alcohol product is observed. When moving to DARA of aromatic ketones, the catalyst is still active; but only low enantioselectivities are obtained (up to 43% *ee*).




**Scheme 1.33:** Reductive amination by chiral Pd-BINAP catalyst.

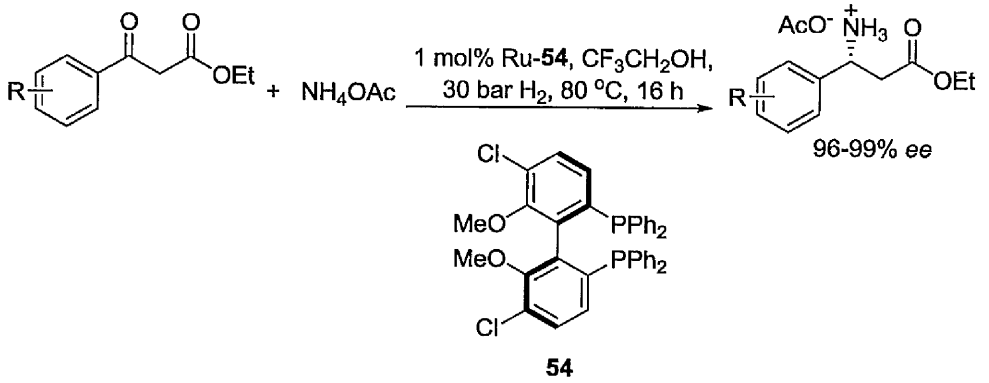
Kadyrov and Börner screened a library of 96 ligands for the rhodium catalysed DARA of α-ketoacids utilised in the synthesis of chiral aminoacids.[112] Best results were obtained when the diphosphine (*R,R*)-DeguPHOS ligand was used, at 1 mol% catalyst loading, 60 bar $H_2$ and room

temperature (Scheme 1.34). Although excellent enantioselectivity (98%) was obtained for DARA of phenyl pyruvic acid with benzylamine, most of the products reported only had moderate *ee* (~50%).



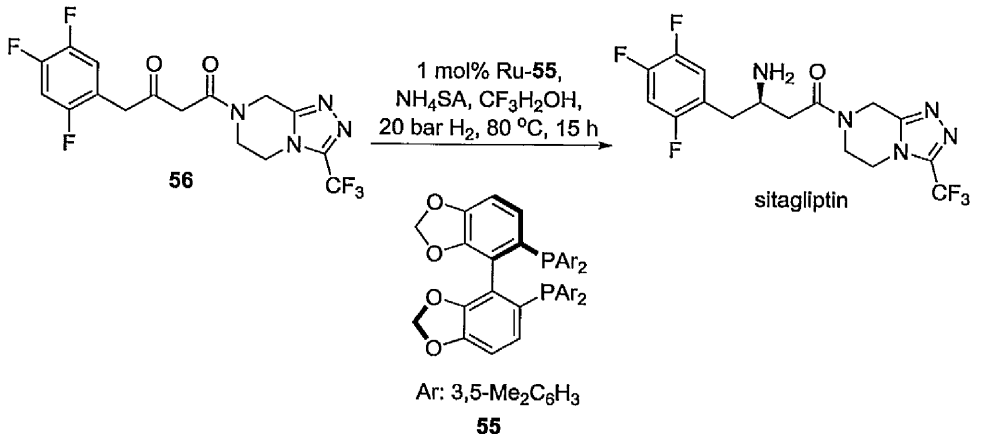

**Scheme 1.34:** Rh-catalysed DARA of α-keto acids.

Apart from chiral α-amino acids, chiral β-amino esters and amides can be synthesised following a reductive amination procedure. Bunlaksananusorn reported the DARA of β-keto esters with a Ru-diphosphine complex under hydrogenation conditions. Under 30 bar $H_2$ and 80 °C with 1 mol% catalyst loading, a series of aryl-substituted β–keto ester was reductively aminated with excellent yields and high enantioselectivities (Scheme 1.35).[113] Steric effects on the phenyl ring can lower the chemoselectivity, resulting in the formation of β-hydroxyester. Only one example of alkyl β–keto ester was reported: reductive amination of ethyl acetylacetonate yielded the corresponding ammonium salt with 96% *ee*.




**Scheme 1.35**: DARA of β-keto esters.

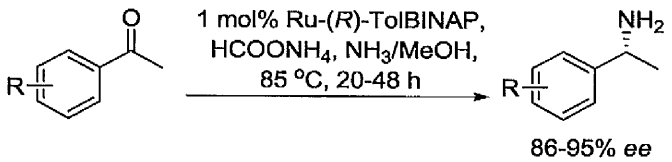
More recently, Steinhuebel reported the first DARA of β-keto amides to the unprotected chiral β–amino amides.[114] A variety of alkyl- and aryl-substituted β–keto amides were converted to the corresponding β–amino amides in high yields and excellent enantioselectivities (95-99% *ee*) under 30 bar $H_2$ at 80 °C with 1 mol% catalyst loading of Ru-DMSegPHOS (Ru-**55**) complex. The addition of ammonium salicylate ($NH_4SA$) eliminates the dimer-like by-product. This methodology was also applied for the synthesis of sitagliptin by DARA of **56** (Scheme 1.36). Sitagliptin is a potent DPP-IV inhibitor for the treatment of type-II diabetes.[115]




**Scheme 1.36**: Synthesis of sitagliptin by reductive amination.

### 1.5.2 Metal-catalysed DARA under TH conditions

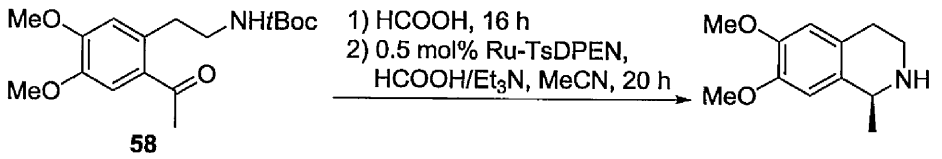
There are only a few examples of DARA with homogeneous catalyst under TH conditions, i.e. using an organic molecule rather than $H_2$ as the hydrogen source. Kadyrov reported the DARA of ketones with a Ru-tolBINAP complex under TH conditions (Scheme 1.37).[116] The reductive amination with ammonium salt of formic acid as a reducing agent is known as the Leuckart-Wallach (LW) reaction.[117] When investigating the effect of additives, the author found that acids accelerated the reaction; however lower enantioselectivities were obtained. The opposite occurred with the addition of ammonia: higher *ee* but lower activity were acquired. Under the best conditions (5-10 eqs. of $HCOONH_4$ in $NH_3$/MeOH at 60-85 °C), the DARA of aromatic ketones proceeded with excellent enantioselectivities. However, the catalyst is not effective for aliphatic ketones, with low conversion and enantioselectivity being reported. To our knowledge, this is the only example of intermolecular DARA under TH conditions.




**Scheme 1.37**: DARA of aromatic ketones under TH conditions.

Noyori developed an excellent Ru(II)-TsDPEN catalyst for ATH of imines under acidic conditions (*vide supra*). In particular, isoquinolines were reduced with excellent yields and enantioselectivities.[118] Wills and co-workers extended this work to a one-pot reductive amination process, where *t*Boc-protected

amine **58** undergoes deprotection, intramolecular cyclization and further reduction of C=N bond (Scheme 1.38).[119] The reaction takes place in sequenced steps: the deprotection occurs under formic acid conditions; then, triethylamine is added to the azeotrope mixture, followed by Ru-TsDPEN complex, as well as anhydrous acetonitrile. For those examples where preformed imines were used, the selectivity was comparable. However, most of the examples reported are essentially racemic.



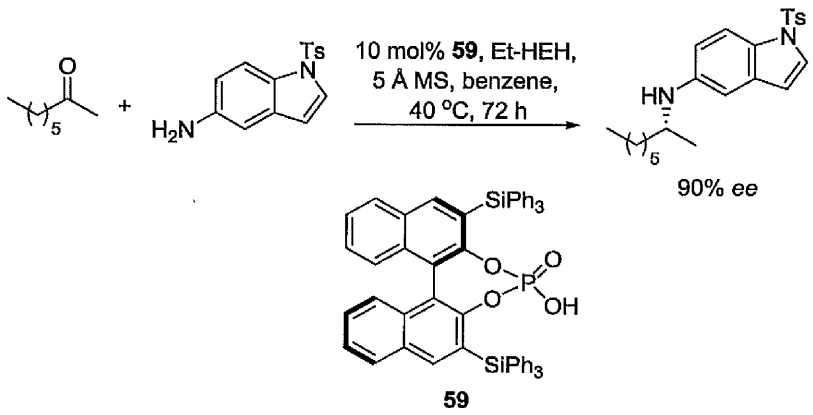

**Scheme 1.38**: Intramolecular DARA under TH conditions.

## 1.6 Organo-catalysed DARA

MacMillan reported the first example of organocatalytic DARA. A chiral Brønsted phosphoric acid is used as catalyst with Et-HEH as reductant. This type of strong chiral phosphoric acids was initially introduced by the Japanese groups of Akiyama[120-121] and Terada[122-124] for the asymmetric addition to aldimines. On the other hand, it had been previously shown that imines can be reduced with HEH in the presence of achiral Brønsted acid catalyst.[125] Prior to this publication, the groups of List[126] and Rueping[127] simultaneously reported the organocatalytic imine reduction with Et-HEH, with the same type of chiral phosphoric acid, although List's results were somehow superior.[126]

A series of aromatic and aliphatic ketones were reductively aminated with derivatives of aniline in the presence of 10 mol% of chiral phosphoric acid **59**

and Et-HEH. Very good yields and enantioselectivities are reported, albeit with long reaction times (24-96 hours) (Scheme 1.39). The combination of Et-HEH with phosphoric acid is chemoselective for imines over other reducible groups, such as ketones, nitro and alkene. This organocatalytic procedure was extended by List and co-workers to the DARA of ketones with benzylamine[128] and DARA of α–branched aldehydes.[129]

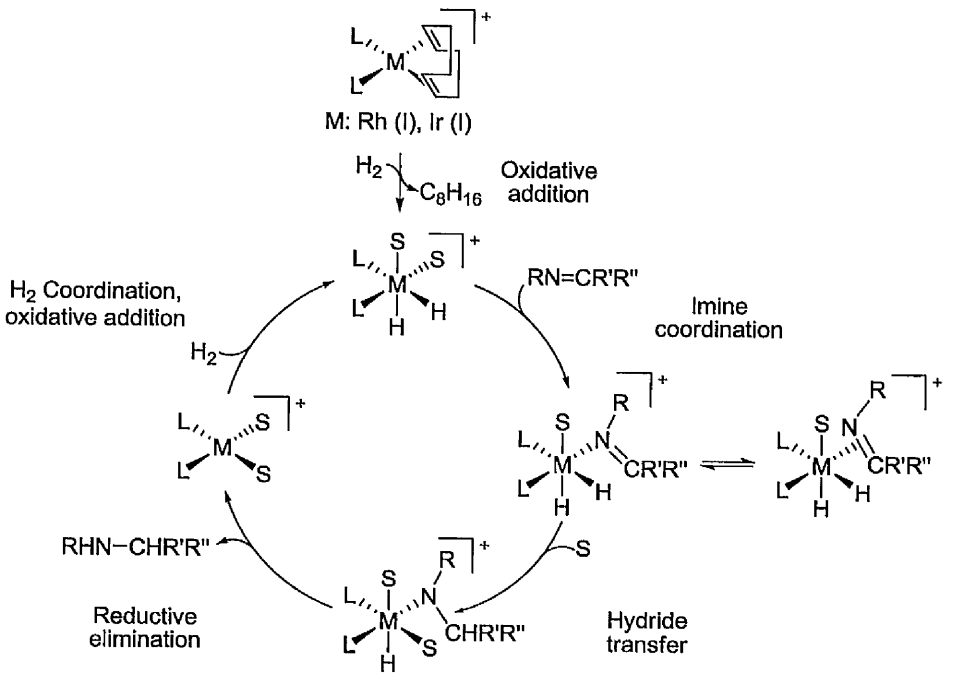



**Scheme 1.39**: Example of organocatalytic DARA.

The catalytic cycle is thought as follows: the imine is formed *in situ*, and subsequently protonated by the chiral **59**. The resulting iminium cation has a lower LUMO than the corresponding imine; therefore it is easier to be reduced by Et-HEH. The iminium cation is stabilised by hydrogen-bonding with the chiral phosphate, which makes the iminium cation facially-biased towards the incoming hydride.[130-131]

## 1.7 Mechanistic considerations for the metal-catalysed imine hydrogenation

Only a few studies of the mechanism of homogeneous hydrogenation of imines have been reported. Two main pathways can be considered for the metal-catalysed imine hydrogenation, the so-called classic and ionic pathways. A simplified representation of the classic pathway involves coordination of hydrogen, oxidative addition, and coordination of the substrate prior to hydride transfer, followed by reductive elimination (Scheme 1.40).




**Scheme 1.40**: General scheme for imine hydrogenation following a classic pathway; L: ligand; S: solvent.

Wilkinson[132] and James[133] studied independently the mechanism for imine hydrogenation with rhodium-phosphine complexes. Wilkinson determined that

alcohol solvents were required, while other polar but non-hydrogen bonding were unsuitable.[132] This suggests that hydrogen bonding may be important. Intramolecular hydrogen bonding between the alcohol solvent and the imine promotes $\eta^2$-C,N-bonding of the imine (Figure 1.21). Attempts to reduce the corresponding iminium cation failed, however. The iminium cation would have little tendency to bond to the metal centre, supporting the idea that the coordination of the imine substrate is required prior to hydride transfer.

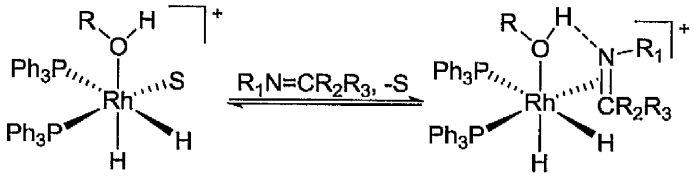
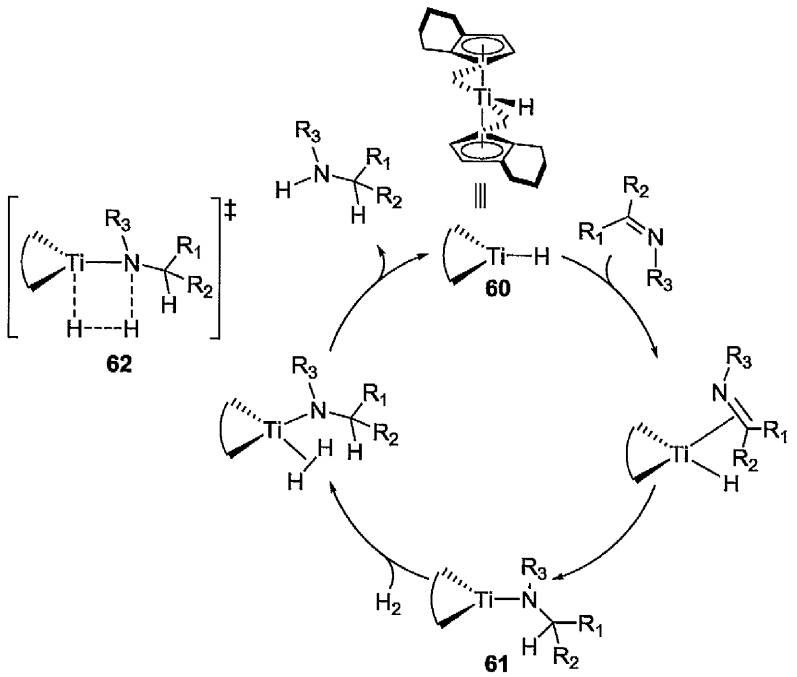



**Figure 1.21**: Intramolecular hydrogen bonding between alcohol solvent and imine substrate.

Later on, studies undertaken by James indicate that imine binding is probably the first step. When rhodium catalysts containing chelating phosphines are used, imine binding is a more facile process than the hydride formation.[133] The use of methanol as the solvent seems to be essential. It reiterates the idea that the alcohol is probably bound to the metal and it facilitates the change from the $\eta^1$ to $\eta^2$ binding of the imine group.

Buchwald *et al.* also reported mechanistic and kinetic studies on imine hydrogenation with their titanocene catalyst.[134] Scheme 1.41 summarises their suggested catalytic cycle, which follows the classic pathway. They proposed the Ti-hydride species **60** as the active catalyst. The imine coordinates to the metal centre through the C=N double bond; this is followed by 1,2-hydride migration on the imine carbon atom to form the amido-titanium(III) complex

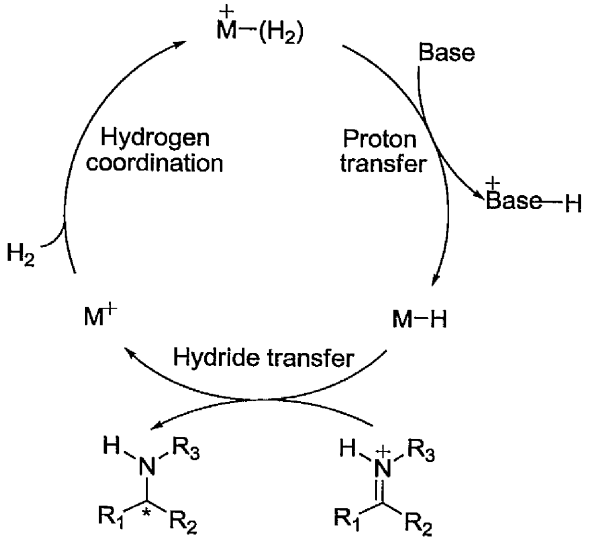
**61**. $H_2$ coordinates to the metal centre, followed by elimination of the amine product via a four-centre transition state **62**, regenerating the active Ti-hydride **60** (A classic inner-sphere mechanism).




**Scheme 1.41**: Catalytic cycle proposed by Buchwald for the titanocene catalyst **60**.

In contrast to the classic pathway shown in the previous examples, the ionic pathway involves no imine coordination, which is represented in Scheme 1.42. This catalytic cycle is usually present when the catalyst is a half-sandwich type complex. After the formation of the active metal species, the actual catalytic cycle is made up of 3 steps: coordination of a $H_2$ molecule, heterolytic cleavage of $H_2$ into a hydride and a proton and subsequent transfer of hydride to the iminium cation. This pathway involves the protonation of the

imine substrate prior to the hydride transfer and does not require the coordination of the substrate to the metal complex (outer-sphere mechanism).




**Scheme 1.42**: Catalytic cycle for an ionic pathway.

The concept of ionic hydrogenation for reduction of imines was introduced by Norton and co-workers in 2001.[135] Although only moderate enantioselectivities were reported for a methyl aryl pyrrolidinium (up to 60% *ee*), they reported the first example of catalytic asymmetric ionic hydrogenation. According to Norton's experiments, the increase of the $H_2$ pressure does not affect either the conversion or the enantioselectivity.[97,135] This supports the hydride transfer to be the turnover-limiting and enantiofacial-determining step. They also followed the reaction by $^1$H NMR, observing the formation of monohydride but not dihydrogen or dihydride species, corroborating the hydride transfer as the turnover-limiting step. In this regard, they studied the effect of the chelate ring size on the hydride transfer step.[136]

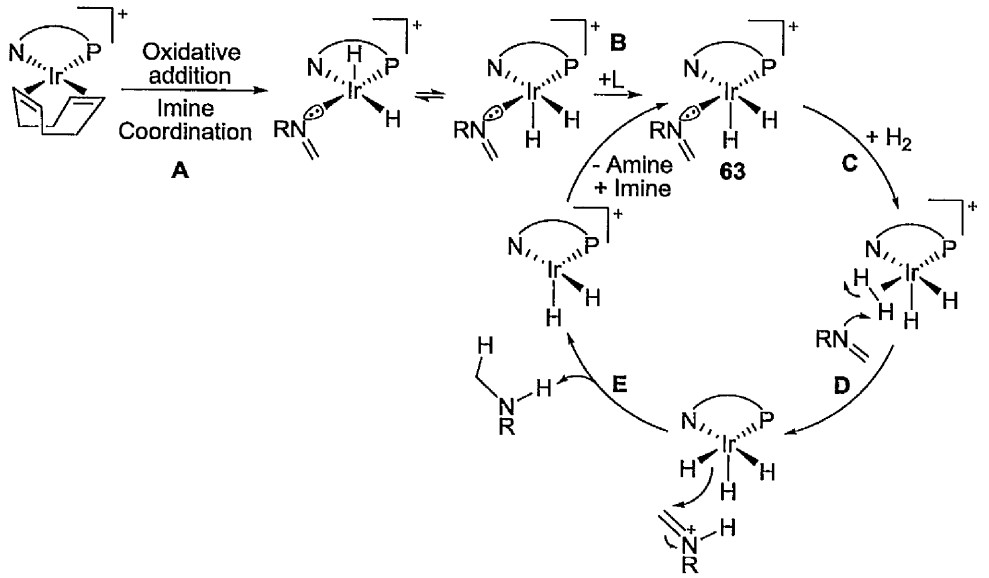
They determined that the smaller the ring, i.e. the smaller the bite angle, the higher the reaction rate. From a steric point of view, the iminium cation has more space to approach the hydride with a smaller chelate ring. From an electronic point of view, the ability to transfer the hydride is mainly determined by the energy of the LUMO for the 16e species formed after the hydride transfer.[137] This type of complex prefers a pyramidal geometry, where a smaller chelate ring will force some additional bending that raises the LUMO energy.

Stoichiometric experiments were run by the groups of Fan[138] and Norton[135] supporting the ionic mechanism: Fan reported no reduction of **50** even in the presence of excess of the hydride; however, the corresponding protonated species reacts smoothly to give the tetrahydroquinoline product. In Norton's experiments it has been determined that the hydride transfer rate is first order for both the Ru-hydride and the iminium cation, being second order overall.[135]

Ikariya's group also reported mechanistic studies for the asymmetric hydrogenation of **6** with Ir-**37**.[65] The role of activation of the imine substrate is addressed with respect to the silver salt, as the presence of excess of $AgSbF_6$ improves not only the activity, but also the enantioselectivity. The substrate is activated by a strong interaction between the imine nitrogen and the Lewis acidic silver centre, observed by a characteristic downfield shift in the imine carbon in $^{13}C\{^1H\}$ NMR experiments, when equimolecular amount of $AgSbF_6$ is added to the imine. Therefore, the silver salt has a dual role: formation of the cationic species for the iridium complexes, as well as enhancement of enantioselectivity by activation of the imine, presumably because N-Ag bond

facilitates the hydride attack to the *Re* face of the imine.

As shown in a previous section (1.3.2), several groups have reported the asymmetric hydrogenation of imines mediated by an Ir-PHOX catalyst. Hopmann and co-workers reported a comprehensive quantum chemical study to determine the preferred Ir-PHOX imine hydrogenation mechanism.[139] Scheme 1.43 shows the possible mechanism, which goes through an Ir(III) catalytic cycle. Firstly, oxidative addition takes place, changing the iridium from Ir(I) to Ir(III). Then, it is assumed that an initial coordination of the imine to the iridium will occur (Step A). A six-coordinated dihydride-Ir-(III) species **63** is formed by binding of an additional ligand (solvent or $H_2$) (Step B). The substrate is then replaced by a $H_2$ molecule (Step C), followed by proton transfer to the imine substrate (step D). Finally, the hydride *trans* to the phosphine ligand is transferred from the Ir(III)-trihydride to the iminium cation (Step E). The hydride transfer is the rate-limiting and enantio-determining step. Interestingly, based on their results, the proposed mechanism is similar to the ionic pathway shown by Norton. Although the coordination of the substrate is involved in the catalytic cycle, it is actually the protonated imine that is the species to be reduced.




**Scheme 1.43**: Mechanism proposed for the imine hydrogenation with Ir-PHOX type catalyst.

## 1.8 Aims of the thesis

This introduction has summarised the best methodologies reported in the literature for the synthesis of chiral amines. In particular, it focuses on the most efficient and selective metal catalysts for asymmetric imine hydrogenation. The groups of Zhang, Blaser and Andersson, among others, have designed excellent ligands and complexes, and applied them to imine hydrogenation, achieving excellent results. However, there is still a need for highly efficient and selective catalysts capable of reducing a wider range of C=N double bonds under mild conditions.

We hope it can be seen that this thesis goes some way to achieving this goal, as new strategies for the synthesis of chiral amines have been developed. Chapter 2 presents an efficient catalyst for DARA of aliphatic ketones, where

the catalysis is effected by the cooperative action of a cationic Ir(III)-diamine complex and its phosphate counterion.

Chapter 3, 4 and 5 were developed naturally from the challenges found in Chapter 2. This cooperative catalysis was not effective for the DARA of ketones with aliphatic amines. Chapters 3 and 4 were born from the efforts to overcome this problem. Chapter 3 presents the synthesis and application of cyclometallated iridium-imine complexes for the hydrogenation of imines. These catalysts are effective for imines from aromatic and aliphatic ketones, as well as aromatic and aliphatic amines. Chapter 4 reports our efforts to develop chiral versions of cyclometallated iridium complexes and their application for the hydrogenation of *N*-benzylimines.

Whilst this cooperative catalysis provides excellent enantioselectivity for the synthesis of α–chiral amines, only moderate enantioselectivity could be achieved when the same methodology was applied to the DARA of α–branched aldehydes, which would lead to β–chiral amines. Besides, these α–branched aldehydes are not commercially available and require prior synthesis and tedious purification. Chapter 5 provides a novel methodology for the synthesis of β–chiral amines, by a one-pot three-step hydroaminomethylation procedure, where a readily accessible styrene is selectively hydroformylated to the corresponding α–branched aldehyde and *in situ* reductively aminated to provide the β–chiral amine with good enantioselectivity.

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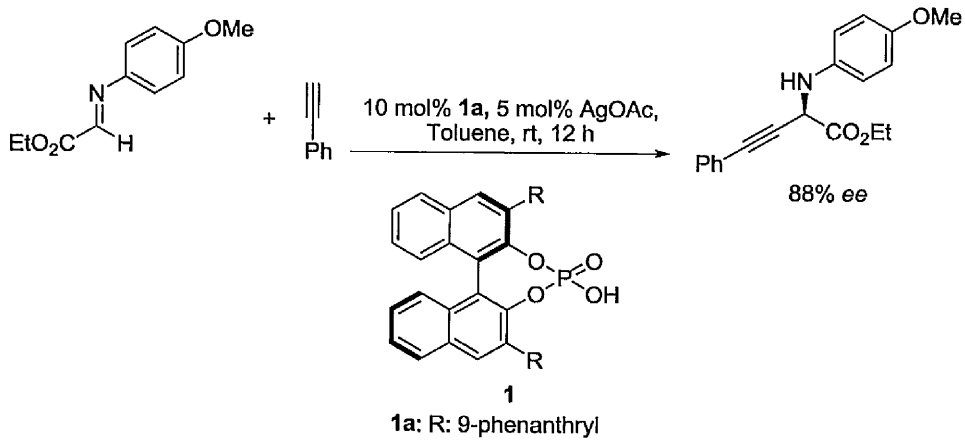
# Chapter 2

# Metal-Brønsted Acid Cooperative Catalysis for Asymmetric Reductive Amination

## 2.1 Introduction

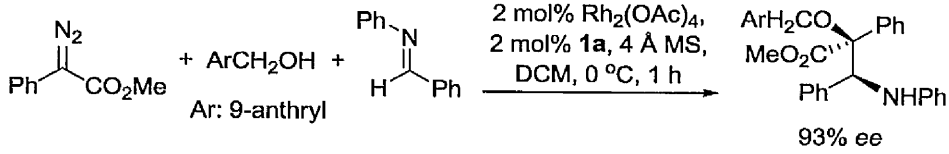
Transition metal catalysis has been established as one of the most useful and powerful tools in organic chemistry.[1] On the other hand, organocatalysis, i.e. small organic molecules acting as catalysts, has become a rapidly growing area in synthetic organic chemistry in the past decade.[2] Very recently, the combination of transition metal catalysis and organocatalysis has gained a lot of attention. It could potentially provide an attractive way for unprecedented transformations, which are not possible with either a transition metal catalyst or organocatalyst alone.[3] In particular, the combination of transition metals with Brønsted acids has proven to be very successful, especially for asymmetric reactions.[3]

An example of this novel dual catalysis was reported by Rueping and co-workers for the alkynylations of α-imino esters.[4] In this regard, a chiral Brønsted acid enantioselectively activates the substrate; then silver-catalysed alkynylation of the activated species takes place. Chiral amino acids were synthesised with good yields and excellent enantioselectivities under mild reaction conditions (Scheme 2.1). No product formation was observed if only the Brønsted acid or the silver acetate was used.




**Scheme 2.1**: Asymmetric metal-Brønsted acid catalysed alkynylation of imines.

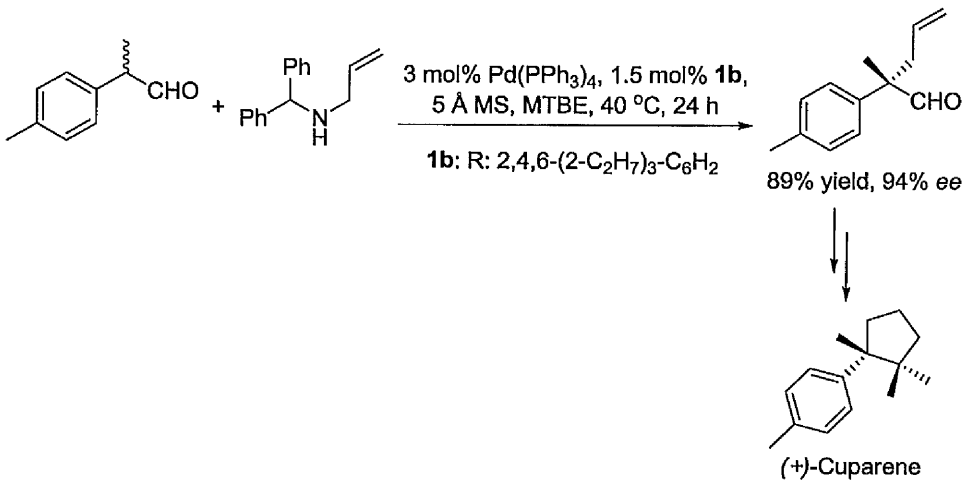
The concept of dual catalysis has also been applied to asymmetric multicomponent reactions. Gong and co-workers reported the enantioselective three-component reaction of diazo compounds and alcohols with imines in the presence of an achiral rhodium complex and a chiral Brønsted acid.[5] In previous work within this group, they had observed that this three component reaction catalysed by $Rh_2(OAc)_4$ was accelerated by proton donors.[5-6] Following this observation, they decided to incorporate a chiral Brønsted acid to develop the corresponding asymmetric version for that reaction. In a similar way to Rueping's work, the role of the chiral acid is the activation of the imine substrate by ion-pairing. An asymmetric Mannich reaction would then take place between the iminium cation and an oxonium ylide, formed *in situ* from a diazoacetate and an alcohol initiated by rhodium catalyst (Scheme 2.2). This procedure allows for the synthesis of β-chiral-α-hydroxyl acid derivatives with a quaternary carbon stereogenic centre with good yields and enantioselectivities up to 99% *ee*.




**Scheme 2.2**: Combination of $Rh_2(OAc)_4$ and chiral Brønsted acid catalyst for a three-component reaction.

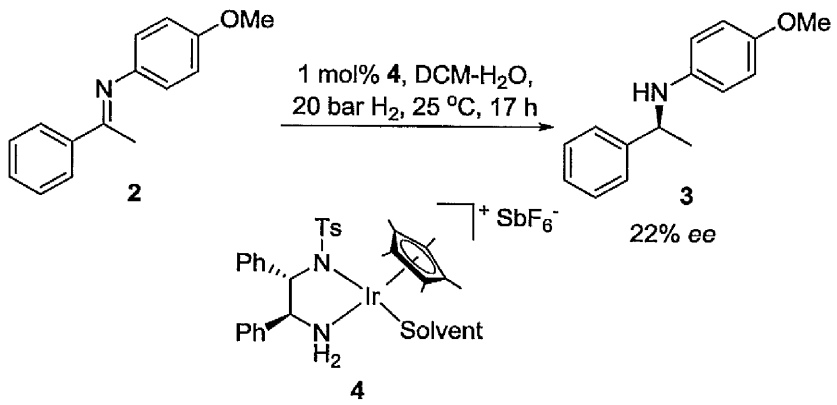
On the basis that the imine could be generated *in situ* from the corresponding aldehyde and amine, Rueping's group then extended the reaction to a four-component reaction, where the extra step comes from the *in situ* imine formation.[7] In this transformation the phosphoric acid **1** would play a dual role: it would not only activate the imine by formation of iminium, but also accelerates the imine formation step.

List and co-workers also used a cooperative catalysis approach for the synthesis of quaternary carbon stereogenic centres. They combined a Pd(0) catalyst with chiral Brønsted acid **1b** for the α-allylation of α-branched aldehydes with an allyl amine (Scheme 2.3).[8] The acid catalyst acts as a proton donor as well as an anionic ligand for the cationic π-allyl Pd(II) complex intermediate, inducing asymmetry. Enantioselectivities in the range of 70-95% were reported. This methodology was effective for the synthesis of a natural product, *(+)*-cuparene.




**Scheme 2.3**: Cooperative catalysis for asymmetric α–allylation of aldehydes.

Previous work within the group showed that cooperative catalysis of Ir-diamine complex with chiral phosphoric acid was effective for the asymmetric hydrogenation of acyclic imines, with excellent yields and enantioselectivities reported.[9] Initially, the group was studying the enantioselective hydrogenation of imines with a Noyori-Ikariya type M-diamine catalyst. While excellent results were reported for the reduction of cyclic imines,[10] only low enantioselectivities were obtained for the hydrogenation of **2** (up to 22% *ee* with **4**) (Scheme 2.4).[9]

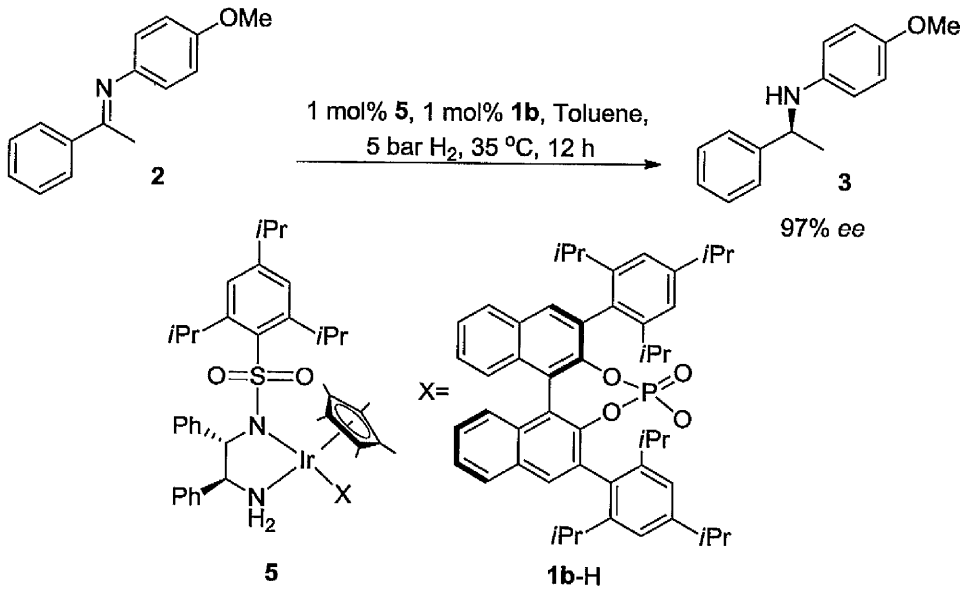



**Scheme 2.4:** Asymmetric hydrogenation of acyclic imine with Rh-diamine catalyst.

Previous to these studies, the groups of Macmillan,[11] Rueping[12] and List[13] have shown that chiral phosphoric acid catalysts such as **1** can induce excellent *ee*'s in imine reduction[12-13] and in DARA[11,14] with HEH, although the reaction times are generally long (up to 3 days). As in most Brønsted acid-catalysed reactions (*vide supra*), the phosphoric acid activates the imine *via* protonation and induces chirality by ion-pairing the resulting phosphate anion and iminium cation. Inspired by this work and by successful examples of cooperative catalysis in the literature, we wondered whether a more versatile catalyst for imine hydrogenation could be constructed by the cooperative action of a $H_2$-activating metal complex and a chiral phosphoric acid.

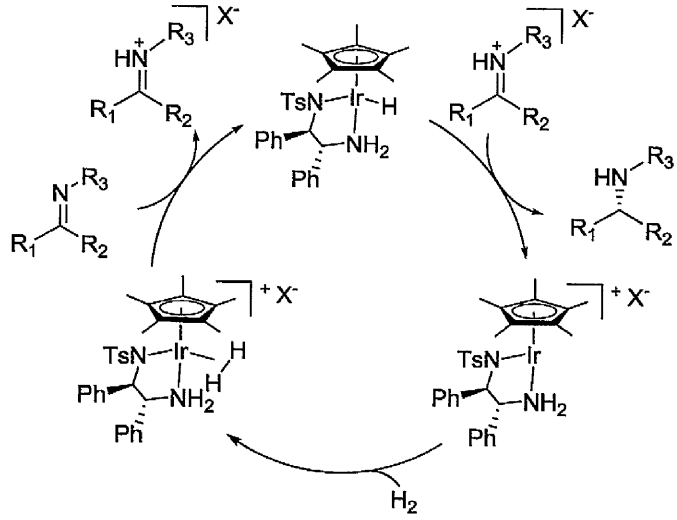
A synergistic effect between the chiral metal complex and the chiral Brønsted acid was indeed demonstrated. The Ir-diamine complex **5** alone led to a low *ee* of 22%, while the combination of chiral Brønsted acid with achiral Ir-diamine complex achieved 73% *ee*.[15] However, the cooperative catalysis of a chiral Brønsted acid with a chiral Ir-diamine complex provided excellent yields

and enantioselectivities (up to 98% *ee*) for a wide range of imines (Scheme 2.5).[9]




**Scheme 2.5**: Combination of chiral Brønsted acid with chiral Ir complex for asymmetric hydrogenation of imines.

The key elements of this cooperative catalysis are illustrated in Scheme 2.6. $H_2$ is activated by the metal complex and heterolytically cleaved, forming an iminium cation (by imine protonation) and an Ir-hydride complex. In a non-polar solvent, the iminium cation ion-pairs, *via* hydrogen bonding, with the chiral phosphate anion,[11-13] and is reduced by hydride transfer from the metal complex (Scheme 2.6). The protonation activates the C=N double bond towards attack by the hydride while ion-pairing aids its enantiodiscrimination by the metal catalyst. This ionic hydrogenation pathway, which involves no coordination of the C=N double bond to the metal, has previously been demonstrated by Norton and co-workers by using iminium tetrafluoroborate salts (See also Scheme 1.42).[16-17]

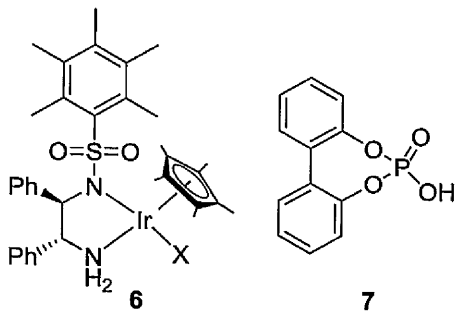



**Scheme 2.6**: Asymmetric hydrogenation of imines *via* metal-counteranion cooperative catalysis.

The excellent results reported prompted us to extend the application of this cooperative catalysis to DARA of ketones. As mentioned in Chapter 1, this is a more desirable approach for the synthesis of chiral amines, because the tedious isolation of imine intermediate is avoided. However, the catalyst must be highly selective for the reduction of C=N over C=O double bonds, as the ketone is present in the reaction media in excess. The development of cooperative catalysis applied to DARA of ketones was undertaken by two PhD students with one focusing on aromatic ketones,[15] while the other on aliphatic ketones. Herein it is described the DARA of aliphatic ketones, for which only few catalysts have been reported.[11,18]

## 2.2 Results and Discussion

### 2.2.1 DARA of aliphatic ketones




**6**

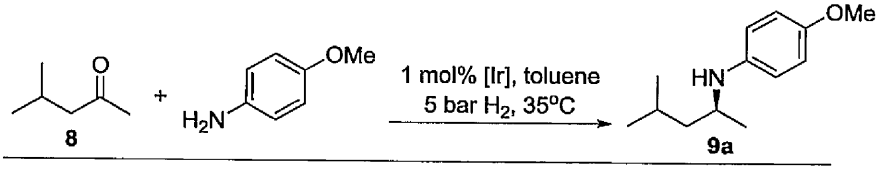
**7**

**6a**: X: Cl
**6b**: X: **7**-H
**6c**: X: **1b**-H

**Figure 2.1:** Structures of chiral Ir(III) catalysts **6** and achiral phosphoric acid **7**.

We started with optimization of the DARA conditions by considering the model reaction of 4-methylpentan-2-one **8** with *p*-anisidine. Table 2.1 summarises the results. While the complex **6a** (Figure 2.1) was inactive in the DARA of **8** (entry 1), exchange of the chloride for a non-coordinating counteranion such as $SbF_6^-$ and $PF_6^-$ allows the reaction to occur, but with low *ee*'s (15 and 35%, respectively) (entries 2 and 3). Changing to the *pseudo*-chiral anion **7**-H, the enantioselectivity rose to 47% (entry 4). This prompted us to search for an Ir(III)-diamine complex containing a chiral counteranion.

**Table 2.1:** Optimisation of conditions for the DARA of **8**.[a]




**8** **9a**

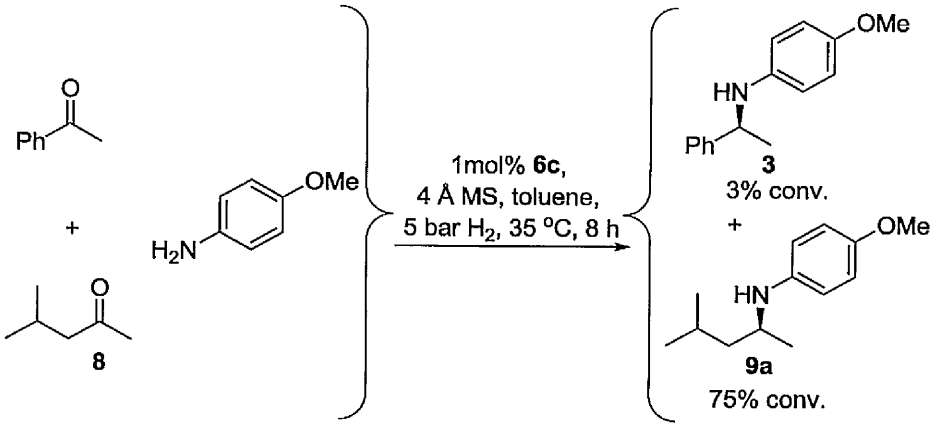
| Entry | [Ir] | Additive | Conv. (%)[b] | *Ee*(%)[c] |
|---|---|---|---|---|
| 1 | **6a** | - | N.R. (17 h) | - |
| 2 | **6a** | $AgSbF_6$ (2 mol%) | 42 (17 h) | 15 *(R)* |
| 3 | **6a** | $AgPF_6$ (2 mol%) | 60 (17 h) | 35 *(R)* |
| 4 | **6b** | - | 11 (17 h) | 47 *(R)* |
| 5 | **6b** | **7** (5 mol%) | 28 (17 h) | 46 *(R)* |
| 6 | **6c** | - | 19 | 84 *(S)* |
| 7 | **6c** | **1b** (1 mol%) | 42 | 85 *(S)* |
| 8 | **6c** | **1b** (5 mol%) | 60 | 86 *(S)* |
| 9 | **6c** | **1b** (8 mol%) | 67 | 89 *(S)* |
| 10 | **6c** | 4 Å MS (50 mg) | 30 | 85 *(S)* |
| 11 | **6c** | 4 Å MS (100 mg) | 50 | 86 *(S)* |
| 12 | **6c** | 4 Å MS | 59 | 86 *(S)* |
| 13 | **6c** | 4 Å MS (200 mg) | 59 | 86 *(S)* |
| 14 | **6c** | **1b** (1 mol%), 4 Å MS | 58 | 85 *(S)* |
| 15 | **6c** | **1b** (5 mol%), 4 Å MS | 63 | 86 *(S)* |
| 16 | **6c** | **1b** (8 mol%), 4 Å MS | 72 | 86 *(S)* |
| 17[d] | **6c** | 4 Å MS | 57 (24 h) | 91 *(S)* |
| 18 | **5** | - | 5 | - |
| 19 | **5** | 4 Å MS | 7 | - |
| 20 | **5** | **1b** (8 mol%) | 50 | 71 *(S)* |
| 21 | **5** | **1b** (8 mol%), 4 Å MS | 60 | 74 *(S)* |
| 22 | **6c** | 4 Å MS | >99 (12 h) | 87 *(S)* |

[a]Reaction conditions: 0.55 mmol of **8**, 0.5 mmol of *p*-anisidine, 1 mol% of catalyst, 2 mL of toluene, 5 bar of $H_2$, 35 °C, 150 mg of 4 Å MS when added unless specified, 6 hours unless specified. [b]Conversion of *p*-anisidine, determined by $^1H$ NMR analysis of the crude product. [c]Determined by HPLC analysis; [d]20 °C.

Thus, as reported before,[9,19] when we moved to the chiral phosphate **1b**-H (**6c**) a 19% conversion and a much higher enantioselectivity of 84% were

observed in 6 hours reaction time (entry 6). Aiming to boost the conversion and *ee*, we then studied the effect of extra acid **1b** and molecular sieves on the DARA. As can be seen, additional **1b** indeed resulted in a faster reaction; but its effect on the enantioselectivity was less significant than that for DARA of aromatic ketones[19] (entries 6 *vs* 7-9). In a similar way, the presence of molecular sieves (MS) increased the reaction rate but not the enantioselectivity (entries 6 *vs* 10-13). We presume that the presence of the MS benefits the ketimine formation by removal of water from the reaction media. Furthermore, we were pleased to discover that in the presence of the MS, the acid **1b** is no longer critical to the DARA rate and *ee* (entry 12 *vs* 16), an observation that is in contrast to what was observed in the DARA of aromatic ketones.[19]

The observations above point to an easier ketimine formation in the DARA of aliphatic ketones. In the case of aromatic ketones, the reaction appears to be limited by this step and hence necessitates both a Brønsted acid and MS, which can catalyse the ketone-amine condensation and help shift the resulting equilibrium by removing water.[9,19] Scheme 2.7 illustrates a competition reaction between an aromatic (acetophenone) and an aliphatic ketone, which led to the predominant DARA of **8**, showing that aromatic ketones are essentially inactive under the conditions employed. When dealing with the aliphatic ketones, we also noted that there was no competition between hydrogenation of ketones over imines; the ketones were not reduced under the DARA conditions.




**Scheme 2.7:** Competitive DARA of an aromatic and an aliphatic ketone with *p*-anisidine.

A quick screening on the ligand showed that catalyst **6c** surpassed **5** in terms of activity and enantioselectivity (entry 16 *vs* 21). In addition, the effect of temperature was also studied. Although a slight increase in the enantioselectivity was observed (entry 17), lowering the temperature to 20 °C afforded only a 57% conversion after 24 hours. Finally, we confirmed that the reaction went to completion in 12 hours reaction time (entry 22). Hence, the optimum reaction conditions are catalyst **6c** and MS (150 mg), and we deemed the addition of extra **1b** unnecessary, avoiding the use of an expensive chiral acid (entry 22).

Next, we explored the application of the optimised reaction conditions to a variety of aliphatic ketones and aromatic amines. As can be seen, a wide range of aliphatic ketones were readily aminated with *p*-anisidine and *m*-anisidine (Table 2.2) and relatively more electron-deficient anilines (Table 2.3) under 5 bar of $H_2$ at 35 °C. The amines **9**, **10** and **11** were obtained with good yields and excellent enantioselectivities in general. Notably, the catalyst tolerates

other reducible functional groups in the substrates, such as terminal (**9i**) and internal alkenes (**9j**, **10h**, **11e**) and highly strained cyclopropyl ring (**9h**, **10i**, **11f**).

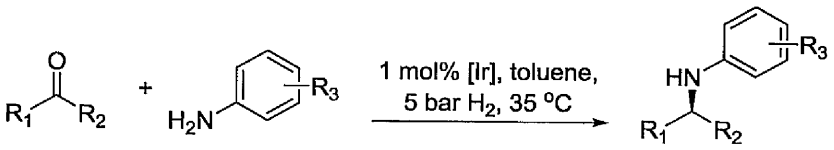
Table 2.2 presents the results for the DARA with *p*-anisidine and m-anisidine. Compared to our results reported for imine hydrogenation at 20 °C (**9a**, **9e**, **9i**),[9] the enantioselectivity is slightly lower, but with the advantage of not isolating the imines.

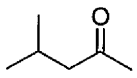
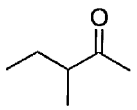
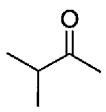
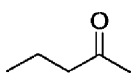
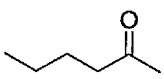
The product **9c** was previously obtained in 84% *ee*,[20] *via* the reduction of the corresponding enantiomerically pure α-sulfinylketimine followed by desulfinylation. **9e** appeared in the DARA with the Pd-(*R*)-BINAP, showing a slightly lower *ee* (76%).[18] The amine **9i** was obtained by Macmillan *et al.* in 90% *ee* in DARA with HEH, but requiring a long reaction time (96 hours).[11] Finally, the amine **9j** has also been reported, as the product of the hydrosilylation of the corresponding imine with 90% *ee*.[21]

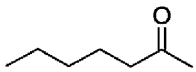
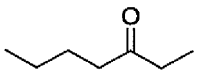
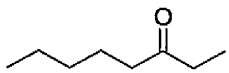
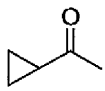
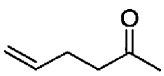
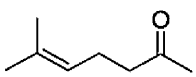
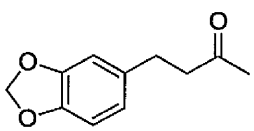
With the sterically more demanding *m*-anisidine, both the yields and *ee*'s remained good, albeit lower than those with *p*-anisidine in most cases (Table 2.2). This lowering in *ee* may stem from a less favoured interaction of the iminium ion with either the metal catalyst or the counteranion or both. Worthy of particular mention is the amine **10c**, where the catalyst is capable of differentiating an isopropyl and a methyl group, affording an excellent 90% *ee*. The amines **10e**, **10h** and **10i** have been previously reported as products for a tandem intermolecular hydroamination-transfer hydrogenation of alkynes.[22] Although similar enantioselectivities were achieved, much longer reaction times appear to be necessary (up to 72 hours).

In general, the products arising from the DARA of alkyl-methyl ketones with *p*-anisidine and *m*-anisidine are obtained with good yields and excellent *ee*'s. However, the enantioselectivity dropped significantly when alkyl-ethyl ketones were aminated (**9f, 9g, 10f, 10g**). Clearly, the catalyst is unable to discriminate efficiently an ethyl from a butyl or pentyl group. This problem might be addressed by modifying the chiral counteranion.

**Table 2.2:** DARA of aliphatic ketones with *p*-anisidine and *m*-anisidine.[a]




| | $R_3$ = *p*-OMe | | | $R_3$ = *m*-OMe | | |
|---|---|---|---|---|---|---|
| Ketone | Product | Yield (%) | *Ee* (%)[b] | Product | Yield (%) | *Ee* (%)[b] |
|  | **9a** | 91 | 87 | **10a** | 72 | 80 |
|  | **9b** | 82 | 96[c] | **10b** | 82 | 96[c] |
|  | | | | **10c** | 86 | 90 |
|  | **9c** | 88 | 90 | **10d** | 77 | 91 |
|  | **9d** | 82 | 93 | **10e** | 85 | 92 |

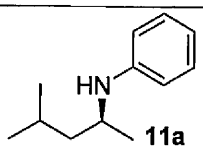
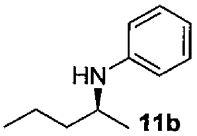
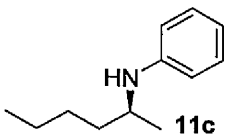
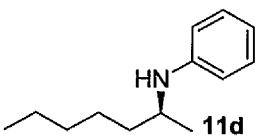
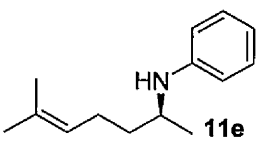
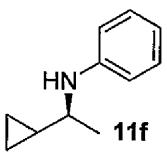
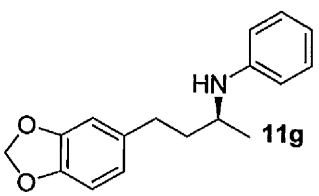
| | | | | | | |
|---|---|---|---|---|---|---|
|  | **9e** | 79 | 91 | | | |
|  | **9f** | 80 | 49 | **10f** | 81 | 61 |
|  | **9g** | 80 | 71 | **10g** | 83 | 64 |
|  | **9h** | 90 | 93 | **10h** | 67 | 82 |
|  | **9i** | 80 | 92 | | | |
|  | **9j** | 89 | 95 | **10i** | 62 | 82 |
|  | **9k** | 85 | 93 | **10j** | 80 | 91 |

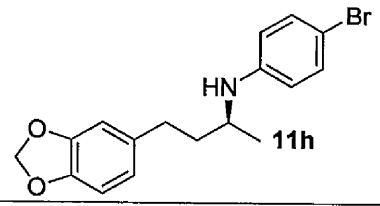
[a] Reaction conditions: 0.55 mmol of ketone, 0.5 mmol of *p*-anisidine, 1 mol% of **6c**, 2 mL of toluene, 150 mg of 4 Å MS, 5 bar of $H_2$, 35 °C, 12-20 hours. [b]Determined by HPLC; *S* configuration, assigned by comparison with the literature.[11] [c]~ 2% d.e.

We then investigated DARA of aliphatic ketones with aniline and more electron-deficient analogues. Amines **11** were obtained with good yields and enantioselectivities (Table 2.3). Of particular note is that *p*-bromoaniline also reacted, giving rise to a decent yield and enantioselectivity, albeit in a longer reaction time (**11h**). Other aliphatic ketones were also aminated with *p*-bromoaniline as well as *p*-chloroaniline, affording 70-90% yields. However, we have not been able to find suitable conditions to separate the enantiomers by HPLC; so they are not included in this chapter. Compounds **11a** and **11b** were previously obtained in DARA with the [$PdBr_2$((*R*)-BINAP)]catalyst,[18]

with only a 51% and 10% *ee*, respectively. A poor enantioselectivity (17%) was also observed for the amine **11b** in the hydrogenation of the corresponding imine with a cationic Ir(I) complex containing a chiral phosphanodihydrooxazole ligand.[23] Similarly, the amine **11d** was previously obtained in only 18% *ee* in the literature.[24]

**Table 2.3:** DARA with aniline and *p*-bromoaniline.[a]

| Entry | Product | Yield (%) | *Ee* (%)[b] |
|---|---|---|---|
| 1 |  **11a** | 80 | 88 |
| 2 |  **11b** | 92 | 94 |
| 3 |  **11c** | 83 | 95 |
| 4 |  **11d** | 83 | 92 |
| 5 |  **11e** | 91 | 91 |
| 6 |  **11f** | 91 | 92 |
| 7 |  **11g** | 95 | 91 |

| | | | |
|---|---|---|---|
| 8[b] |  **11h** | 70 | 84 |

[a]Same conditions as those in Table 2.2, except with 0.5 mmol aniline.
[b]Determined by HPLC. [c]0.5 mmol *p*-bromoaniline, 30 hours.

To further appreciate how steric effects affect the cooperative DARA, we compared the amination of the ketones in Figure 2.2 with *p*-anisidine. As can be seen, with increasing steric hindrance near the carbonyl carbon, the DARA becomes slower, and no amination was observed with the sterically most demanding *tert*-butylmethyl ketone, even after 24 hours. This reduction in rate is most likely a result of increased difficulty in hydride transfer. The enantioselectivity is, however, more difficult to explain, as it does not follow the trend of reaction rate and is highest with a sterically bulky ketone (entries 2 *vs* 1 and 3, Table 2.2). This is probably a reflection of the enantioselectivity being controlled by both the Ir(III) catalyst and its counteranion. The former is responsible for hydride delivery and would be expected to respond to steric effects in the manner observed.

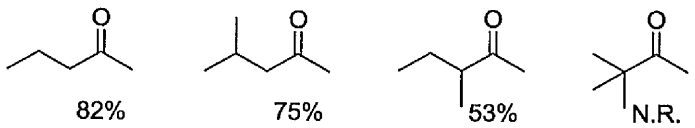
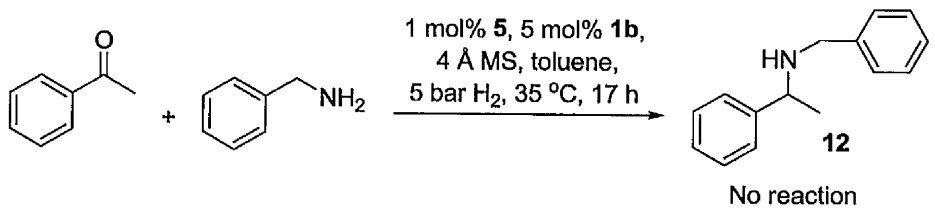



**Figure 2.2:** Conversion observed in the DARA with 1 mol% **6c** at 5 bar $H_2$ and 35 °C in 8 hours.

### 2.2.2 DARA with aliphatic amine

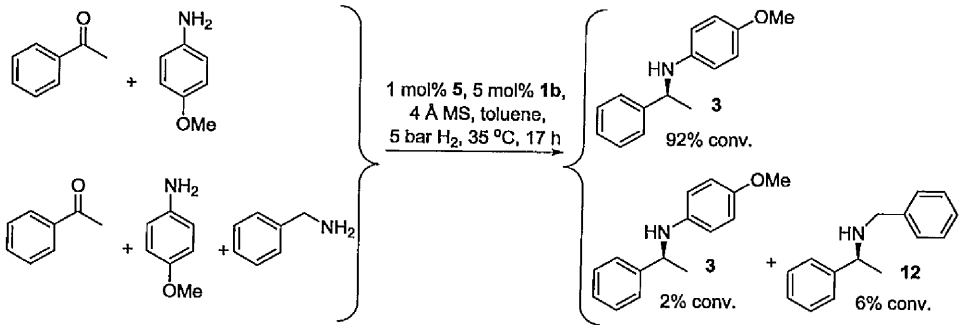
After the excellent results obtained for DARA with aromatic amines,[19,25] we then decided to extend the scope to DARA with aliphatic amines. The benzyl protecting group can be easily removed by hydrogenolysis with Pd/C, offering an attractive route for the synthesis of chiral primary amines.[26] There are only few examples in the literature for the asymmetric hydrogenation of *N*-benzyl imines where high enantioselectivity is reported.[27-30] There are even fewer examples for the DARA with *N*-benzyl amines. As mentioned in Chapter 1, Kadyrov and Börner reported the Rh-catalysed DARA of α–keto acids for the synthesis of α-*N*-benzylamino acids with moderate to good enantioselectivities (50-91% *ee*).[31] List *et al.* reported the organocatalytic DARA of ketones with benzylamine using **1a** as the catalyst, with enantioselectivities in the range of 26-88% *ee*.[26]

We applied the optimised conditions for DARA with *N*-aryl amines. To our disappointment, treatment of acetophenone with benzylamine in those conditions gave almost no conversion to amine **12** (Scheme 2.8).




**Scheme 2.8:** Attempt of DARA with an aliphatic amine using metal-Brønsted acid bifunctional catalyst **5**.

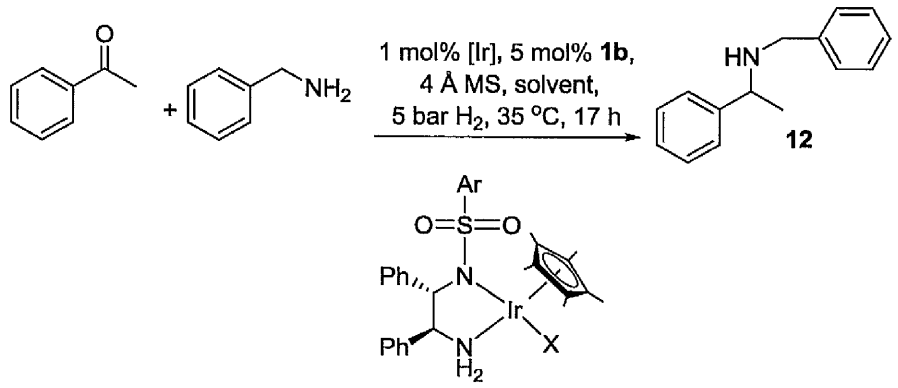
We reasoned that the high basicity of benzylamine (pKa: 9.34)[32] could lead to deactivation of the catalyst, presumably by either coordination to the vacant site or by deprotonation of the ligand leading to the inactive 16e amido complex.[9] To support this idea, we compared the DARA of acetophenone with *p*-anisidine in the absence and in the presence of benzylamine. When benzylamine is present, there is negligible conversion to any of the possible hydrogenation products, supporting the idea of the catalyst being poisoned by the amine (Scheme 2.9).




**Scheme 2.9**: Competition reaction of DARA between aromatic and aliphatic amine.

We then considered changing the solvent in order to discourage the deactivation of the catalyst by benzylamine. The results are shown in Table 2.4. Neither DCM (entry 2) nor a variety of alcohol solvents (entries 3-5) allowed the imine reduction. Only when $CF_3CH_2OH$ (TFE) was used as solvent, the reduction of the imine occurred (entry 6). Unfortunately, the amine product was obtained as a racemic mixture. The modification of the chiral ligand in the complex did not show any improvement (entries 6-9), even when the ligand possessed an extra stereogenic centre (entry 9).

**Table 2.4**: Solvent and catalyst effect on the DARA of acetophenone with benzyl amine.[a]




**13**: X: **1b**-H
**13a**: Ar: 3,5-$(CF_3)_2(C_6H_3)$
**13b**: R: 2-(*S*)-Camphor

| Entry | [Ir] | Solvent | Yield **15** (%)[c] | *Ee* (%)[d] |
|---|---|---|---|---|
| 1 | **6c** | Toluene | 11 | N.D. |
| 2 | **6c** | DCM | N.R. | - |
| 3 | **6c** | MeOH | 6 | N.D. |
| 4 | **6c** | 1,3-Propanediol | N.R. | - |
| 5 | **6c** | Isopropanol | N.R. | - |
| 6 | **6c** | TFE | 91 | 0 |
| 7[b] | **5** | TFE | 52 | 0 |
| 8[b] | **13a** | TFE | 44 | 0 |
| 9[b] | **13b** | TFE | 42 | 0 |

[a]Reaction conditions: 0.3 mmol of acetophenone, 0.25 mmol of benzylamine, 1 mol% of catalyst, 5 mol% of **1b**, 2 mL of toluene, 150 mg of 4 Å MS, 5 bar of $H_2$, 35 °C, 17 hours. [b]8 h. [c]N.R., no reaction. [d]N.D., not determined.

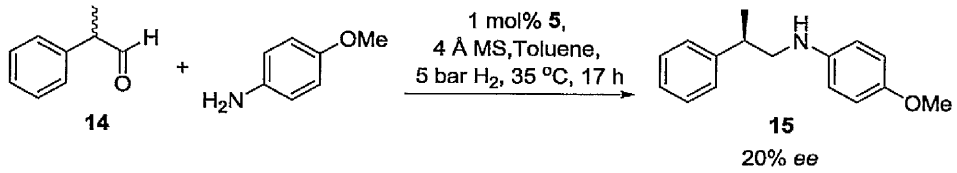
The lack of enantiodiscrimination suggests that neither the chiral counterion nor the chiral ligand participate in the reduction step. It is understood that the counterion ion-pairs with the imine substrate by hydrogen bonding; as expected, a polar protic solvent would not favour the ion-pairing. Furthermore, we propose that the chiral ligand may be displaced in the metal complex by the imine intermediate, which might coordinate to the metal centre

by cyclometallation. A parallel work developed within the group showed that an Ir-imine cyclometallated complex was the active catalyst in the reductive amination by transfer hydrogenation.[33]

### 2.2.3 DARA of α–branched aldehyde

With the excellent results obtained for DARA of ketones in hand for the synthesis of α–chiral amines, we then decided to explore the potential of this metal-Brønsted acid cooperative catalysis for the DARA of α–branched aldehydes. This would result in a new methodology for the synthesis of β–chiral amines. To our knowledge, this methodology has only previously described by List and co-workers, using **1b** as the organocatalyst and Et-HEH as the hydrogen source.[14]

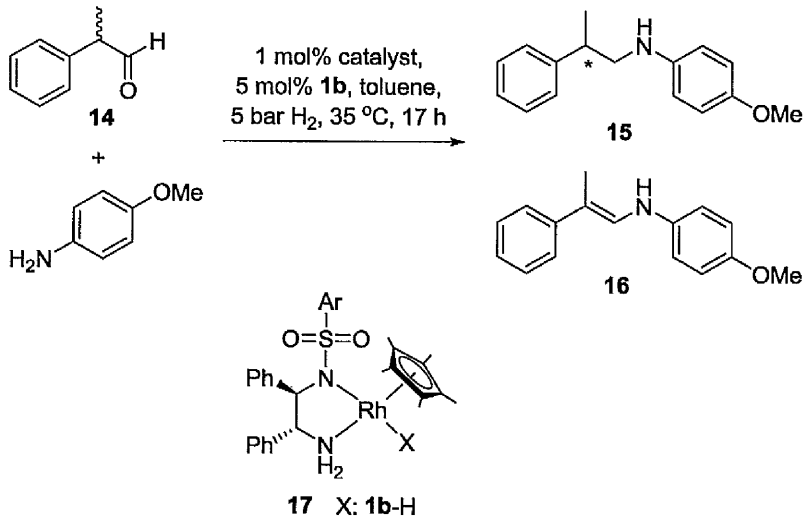
As a starting point for our study, we applied the DARA conditions for aliphatic ketones to the reaction of α–branched aldehyde **14** with *p*-anisidine. However, only 70% conversion and 20% *ee* were obtained after running the reaction overnight (Scheme 2.10). To improve this preliminary result, we studied the effect of acid catalyst, metal centre, ligand, solvent and temperature for DARA of α–branched aldehyde **14** with *p*-anisidine. The results are outlined below.




**Scheme 2.10**: Catalyst applied for the DARA of α–branched aldehyde **11**.

The effect of the metal centre was studied. $[RhCp^*Cl_2]_2$ showed to be superior over the iridium analogue and $[Ru(p\text{-cymene})Cl_2]_2$ (Table 2.5). Enamine **16** is not reduced in the presence of the ruthenium dimer (entry 1) and only 10% *ee* was obtained when $[IrCp^*Cl_2]_2$ was used as a catalyst (entry 2). The effect of the chiral diamine ligand was then studied using rhodium as the metal centre (Table 2.5, entries 4-7). More electron-deficient ligands provided an increase in enantioselectivity (entries 6 and 7). However, this increase was insignificantly beneficial (entries 4, 5 *vs* 6, 7).

**Table 2.5**: Effect of metal centre.[a]




**17** X: **1b**-H

**17a**: Ar: 4-MeO($C_6H_4$)
**17b**: Ar: 2,4,6-($C_3H_7$)$_3$($C_6H_2$)
**17c**: Ar: 2-naphthyl
**17d**: Ar: 3,5-($CF_3$)$_2$($C_6H_3$)

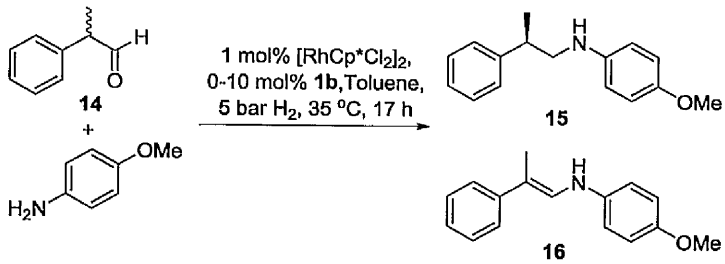
| Entry | Catalyst | Conv. to **15** (%)[b] | Conv. to **16** (%)[b] | *Ee* **15** (%)[c] |
|---|---|---|---|---|
| 1 | [Ru(*p*-cymene)$Cl_2$]$_2$ | 2 | 71 | N.D. |
| 2 | [IrCp*$Cl_2$]$_2$ | 74 | 16 | 10 |
| 3 | [RhCp*$Cl_2$]$_2$ | 70 | 28 | 30 |
| 4 | **17a** | 69 | 31 | 35 |
| 5 | **17b** | 83 | 17 | 36 |
| 6 | **17c** | 84 | 16 | 39 |
| 7 | **17d** | 85 | 15 | 42 |

[a]Reaction conditions: 0.3 mmol of **14**, 0.25 mmol of *p*-anisidine, 1 mol% of catalyst, 5 mol% of **1b**, 2 mL of toluene, 5 bar of $H_2$, 35 °C, 17 hours. [b]Determined by $^1$H NMR. [c]Determined by HPLC; N.D., not determined.

Table 2.6 shows the effect of the presence of Brønsted acid in the reaction. As observed for DARA of aromatic ketones, the presence of acid had a positive effect on the conversion (entries 2-4). It was understood that the acid would catalyse the imine formation, as well as the imine reduction. However, the enamine intermediate is formed without the need of acid catalysis (entry 1),

suggesting that the Brønsted acid exclusively catalyses the reduction step. Although best results were obtained when 10 mol% of **1b** was used (entry 4), we continued the following screening with only 5 mol%, to ensure the catalyst loading remains low.

**Table 2.6**: Effect of Brønsted acid.[a]



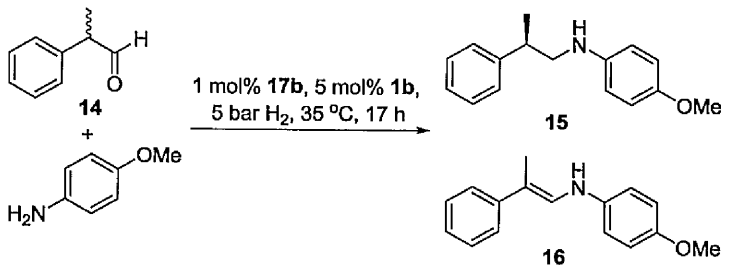

| Entry | mol% **1b** | Conv. to **15** (%)[b] | Conv. to **16** (%)[b] | *Ee* **15** (%)[c] |
|---|---|---|---|---|
| 1 | - | 0 | 91 | N.D. |
| 2 | 1 | 22 | 75 | 24 |
| 3 | 5 | 70 | 28 | 30 |
| 4 | 10 | 90 | 8 | 34 |

[a]Reaction conditions were the same as those in Table 2.6 except 1 mol% $[RhCp^*Cl_2]_2$ and 0-10 mol% **1b**. [b]Determined by $^1H$ NMR. [c]Determined by HPLC; N.D., not determined.

We then run a solvent screening (Table 2.7). Water and THF do not facilitate the reduction of **16** (entries 1 and 2). Methanol, a polar protic solvent, led to a racemic mixture of the imine (entry 3). It is understood that the corresponding anion of **1b** forms an ion-pair with the iminium cation by hydrogen bonding, and polar protic solvents do not facilitate the ion-pairing. Halogenated solvents provided higher selectivity compared to toluene (entries 6-9 *vs* 10). However, the best enantioselectivity was obtained with an aprotic solvent MTBE (entry 11), although only 53% *ee* was reached. The presence of

MS and reaction at lower temperature were also studied. However, the enantioselectivity remained moderate (up to 53% *ee*). Therefore, a scope of substrates was not developed.

**Table 2.7**: Solvent screening.




| Entry[a] | Solvent | Conv. to **15** (%)[b] | Conv. to **16** (%)[b] | *Ee* **15** (%)[c] |
|---|---|---|---|---|
| 1 | $H_2O$ | 0 | 100 | N.D. |
| 2 | THF | 11 | 77 | N.D. |
| 3 | MeOH | 73 | 11 | < 1 |
| 4 | MeCN | 40 | 60 | 16 |
| 5 | DCM | 74 | 19 | 46 |
| 6 | DCE | 56 | 44 | 39 |
| 7 | $CHCl_3$ | 72 | 23 | 45 |
| 8 | $CH_2Br_2$ | 50 | 43 | 46 |
| 9 | Chlorobenzene | 79 | 21 | 40 |
| 10 | Toluene | 79 | 21 | 36 |
| 11 | MTBE | 82 | 17 | 53 |

[a]Reaction conditions were the same as those in Table 2.6 except 1 mol% **17b**. [b]Determined by $^1$H NMR. [c]Determined by HPLC; N.D., not determined.

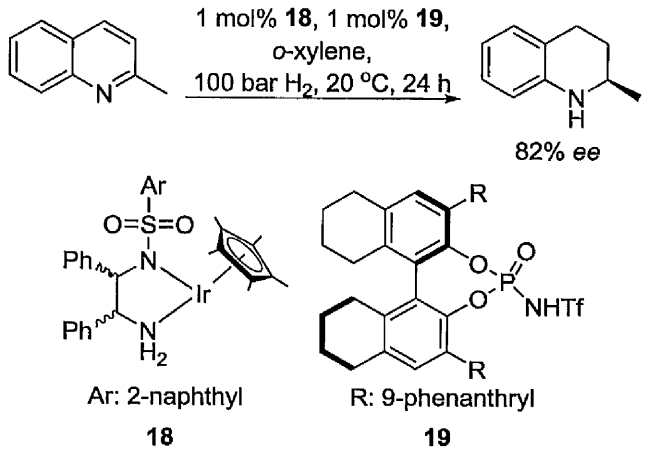
## 2.3 Conclusions and future work

In conclusion, we have developed an efficient catalyst for DARA of ketones. The corresponding catalyst, formed by the combination of a chiral metal complex and a chiral phosphate counteranion, allows excellent yields

and enantioselectivities for a wide range of aliphatic ketones and aromatic amines. In conjunction with the work on aromatic ketones also developed within the group, this catalyst appears to be one of the best for DARA. The reaction works at low hydrogen pressure and mild temperature. Investigations into the mechanism of the reaction are currently undergoing by other members of this research group.

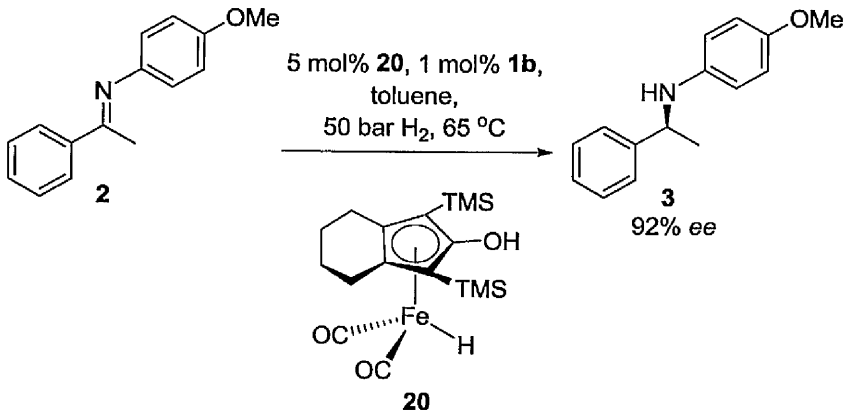
Several limitations have been found, however. Only moderate enantioselectivities are obtained for the DARA of α–branched aldehydes. It is more difficult to induce selectivity on these substrates, as the chiral centre formed does not form part of the double bond reduced. In addition, the DARA with aliphatic amines is not possible under the general conditions developed due to deactivation of the catalyst. The reaction can only take place in TFE; but only racemic mixtures were obtained.

The publication of this cooperative Ir-phosphate catalysis for the DARA of ketones has prompted other research groups to extend this chemistry to other substrates and/or greener and cheaper catalysts. As shown in Chapter 1, Rueping and co-workers studied the asymmetric hydrogenation of quinolines with the combination of a racemic Ir-complex and a chiral phosphoramide. However, only moderate enantioselectivities (up to 82% *ee*) were reported (Scheme 2.11).[34]




**Scheme 2.11**: Asymmetric hydrogenation of quinolines with racemic metal catalyst and chiral N-triflylphosphoramides.

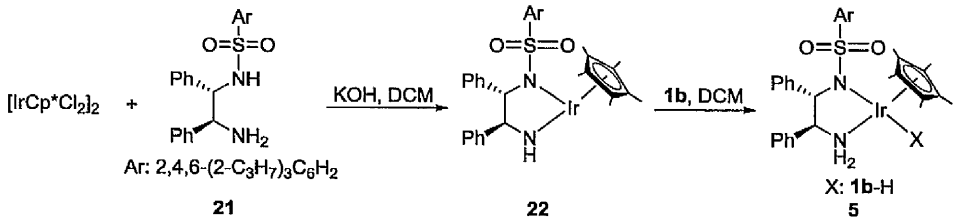
More recently, Beller and co-workers reported the asymmetric hydrogenation of acyclic imines by the cooperative catalysis of Knölker's complex **20** and phosphoric acid **1b**, with high enantioselectivities reported (Scheme 2.12).[35] This leads to a cheaper and more eco-friendly cooperative catalyst for the synthesis of chiral amines by asymmetric hydrogenation.




**Scheme 2.12**: Asymmetric hydrogenation of imines with cooperative Fe-complex and chiral phosphoric acid.

## 2.4. Experimental

### General procedure for the synthesis of complex 5 and its derivatives




To an oven-dried Schlenk tube equipped with stir bar was added $[IrCp^*Cl_2]_2$ (0.3 mmol) and (*S,S*)-**21** (0.6 mmol). The Schlenk tube was then degassed 3 times with $N_2$. Freshly distilled DCM was added (2 mL). An excess of aqueous solution of KOH was then added.[36] The reaction mixture was left stirring at room temperature for 3 hours. The mixture was washed with $H_2O$ (2 × 5 mL). The organic layer was dried over $MgSO_4$, filtered through celite and concentrated to afford the crude product. 16e amido Ir complex (*S,S*)-**22** was used in the following step without further purification.

A solution of **1b** (113 mg, 0.15 mmol) in freshly distilled DCM (5 mL) was added dropwise into a solution of the corresponding (*S,S*)-**22** (0.15 mmol) in DCM (5 mL) under a nitrogen atmosphere at room temperature over a period of 30 minutes. After the solution was stirred for another 30 minutes, the solvent was removed *in vacuo*. The resulting red solid was used for hydrogenation without further purification. **6c** complex was synthesised following a similar method.

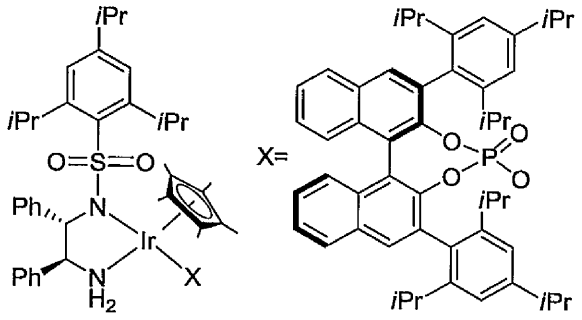
### General procedure for the DARA of ketones:

To a glass liner equipped with a stir bar was added 4 Å MS (150 mg), aliphatic ketone (0.55 mmol), amine (0.5 mmol), catalyst (5 μmol) and distilled

toluene (2 mL). The glass liner was then placed into an autoclave, followed by degassing with $H_2$ three times. The hydrogenation was carried out at 5 bar $H_2$ with stirring at 1000 rpm, 35 °C for 12–30 hours. The hydrogen gas was then carefully released in a fume hood and the solution was filtered, transferred to a flask, and concentrated to afford the crude product. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (15/1) yielded the desired amine product.

## 2.5. Analytical data

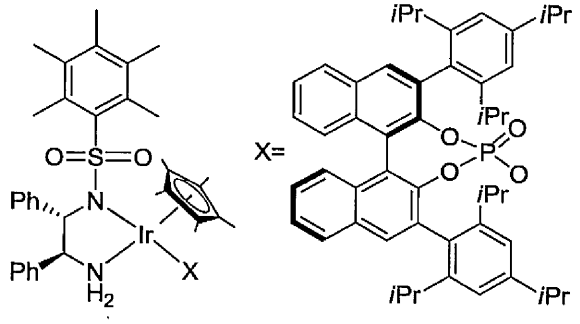
Compounds **5**, **6c**, **9b**, **9f-h**, **9k**, **10a-d**, **10f-g**, **10j**, **11e-h** are new compounds.




**5**

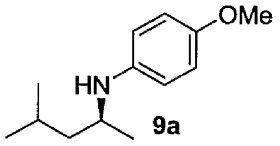
**5** was obtained as a red solid according to the general procedure.
**Mp** = 210°C dec.
**$^1$H NMR** ($CDCl_3$, 400 MHz) δ 0.92 (d, $J$ = 6.8 Hz, 12H), 1.11 (d, $J$ = 6.8 Hz, 12H), 1.16 (d, $J$ = 7.2 Hz, 12H), 1.18 (d, $J$ = 7.2 Hz, 6H), 1.24 (d, $J$ = 7.2 Hz, 12H), 2.02 (s, 15H), 2.54-2.62 (m, 2H), 2.68-2.79 (m, 2H), 2.85-2.91 (m, 2H), 2.94 (brs, 1H), 3.73-3.80 (m, 2H), 3.93-3.95 (m, 1H), 5.36 (br, 1 H), 6.83 (s, 2H), 6.99 (s, 2H), 7.03 (s, 2H), 7.09-7.17 (m, 8H), 7.21-7.30 (m, 6H), 7.40 (t, $J$ = 6.8 Hz, 2H), 7.77 (s, 2H), 7.85 (d, $J$ = 8.0 Hz, 2H);
**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 10.8, 23.8, 24.1, 24.5, 24.7, 25.5, 26.9, 29.7, 31.1, 31.2, 34.4, 34.7, 73.2, 81.7, 85.7, 120.3, 121.0, 123.0, 124.9, 125.8, 126.7, 127.0, 127.3, 127.8, 128.3, 128.4, 130.7, 132.0, 133.2, 133.3, 133.4, 133.7, 134.5, 146.5, 147.4, 148.0, 148.6, 150.8, 151.0;
**$^{31}$P NMR** ($CDCl_3$, 162 MHz) δ 7.0;
**IR** (neat) 3660 (w), 2977 (s), 2889 (m), 2364 (w), 2337 (w), 1388 (m), 1095 (s), 964 (m) $cm^{-1}$;

**HRMS** (ES) for $[C_{39}H_{52}N_2O_2S^{193}Ir]^+$ [M – $C_{50}H_{56}O_4P]^+$: Calcd: 805.3379; Found: 805.3391.




**6c**

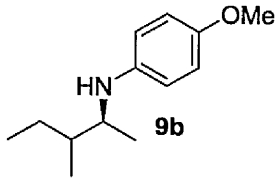
**6c** was obtained as a red solid according to the general procedure.
**Mp** = 205°C dec.
**$^1$H NMR** ($CDCl_3$, 400 MHz) δ 0.94 (d, $J$ = 6.8 Hz, 12H), 1.12 (d, $J$ = 6.8 Hz, 6H), 1.20 (d, $J$ = 7.2 Hz, 6H), 1.26 (d, $J$ = 6.8 Hz, 12H), 1.99 (s, 6H), 2.00 (s, 6H), 2.06 (s, 15H), 2.16 (s, 3H), 2.58-2.64 (m, 2H), 2.70-2.79 (m, 2H), 2.86-2.93 (m, 2H), 2.99 (brs, 1H), 3.95 (s, 1H), 4.00 (s, 1H), 5.17 (br, 1H), 7.00 (s, 2H), 7.04 (s, 2H), 7.13-7.31 (m, 12H), 7.40-7.44 (m, 4H), 7.99 (s, 2H), 7.86 (d, $J$ = 8.0 Hz, 2H);
**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 9.3, 15.7, 16.4, 17.7, 22.3, 22.9, 23.2, 23.9, 25.3, 29.6, 33.1, 77.9, 78.8, 84.1, 119.2, 121.3, 123.0, 124.0, 124.8, 124.9, 125.8, 126.0, 126.1, 126.5, 128.9, 130.2, 131.4, 131.6, 131.9, 132.0, 133.9, 135.8, 143.7, 145.9, 146.1, 146.8;
**$^{31}$P NMR** ($CDCl_3$, 162 MHz) δ 6.9;
**IR** (neat) 3652 (w), 2977 (s), 2889 (m), 2360 (w), 2333 (w), 1384 (m), 952 (m), 632 (s) $cm^{-1}$;
**HRMS** (ES) for $[C_{35}H_{44}N_2O_2S^{193}Ir]^+$ [M – $C_{50}H_{56}O_4P]^+$: Calcd: 749.2753; Found: 749.2733.




**9a**

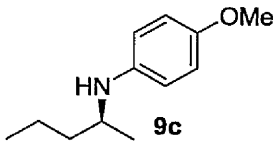
4-Methoxy-*N*-(4-methylpentan-2-yl)aniline.[9] The product (94 mg, 91% yield, 87% *ee*) was obtained according to the general procedure as a colourless oil from 4-methylpentan-2-one (55 mg, 0.55 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 12 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.83 (d, $J$ = 6.6 Hz, 3H), 0.85 (d, $J$ = 6.6 Hz, 3H), 1.05 (d, $J$ = 6.3 Hz, 3H), 1.15 (dt, $J$ = 13.7, 6.9 Hz, 1H), 1.37 (dt, $J$ = 13.7, 6.9 Hz, 1H), 1.62-1.72 (m, 1H), 2.92 (brs, 1H), 3.31-3.39 (m, 1H), 3.66 (s, 3H), 6.45-6.49 (m, 2H), 6.67-6.71 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.5, 22.9, 23.4, 25.5, 47.4, 48.0, 56.2, 115.1, 115.4, 142.3, 152.2;
**IR** (neat) 3656 (w), 2977 (m), 2885 (w), 1512 (s), 1234 (m), 1037 (m), 818 (m) $cm^{-1}$;

**HRMS** for $C_{13}H_{22}NO$ $[M+H]^+$: Calcd: 208.1701; Found: 208.1705;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 99:1, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 13.5 min (minor), $t_R$ = 14.6 min (major).



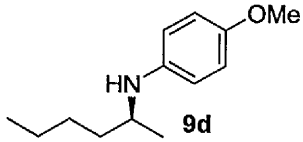

**9b**

4-Methoxy-*N*-(3-methylpentan-2-yl)aniline. Mixture of diastereoisomers 51:49. The product (85 mg, 82% yield, 96% *ee*) was obtained according the general procedure as a colourless oil from (+/-)-3-methylpentan-2-one (55 mg, 0.55 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.84-0.94 (m, 6H), 1.03 (d, *J* = 8.6 Hz, 1.5H), 1.07 (d, *J* = 7.6 Hz, 1.5H), 1.13-1.25 (m, 1H), 1.42-1.63 (m, 2H), 3.31-3.40 (m, 1H), 3.74 (s, 3H), 6.55-6.58 (m, 2H), 6.74-6.78 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 12.3(7), 12.4(3), 14.0, 15.7, 16.0, 17.6, 25.2, 27.0, 38.6, 39.5, 53.5, 54.1, 56.2, 115.2, 115.4, 142.5, 152.2;
**HRMS** for $C_{13}H_{22}NO$ $[M+H]^+$: Calcd: 208.1701; Found: 208.1697;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 99:1, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 12.0 min (d1, minor), $t_R$ = 12.9 min (d2, minor), $t_R$ = 13.8 (d1, major), $t_R$ = 14.8 (d2, major).




**9c**

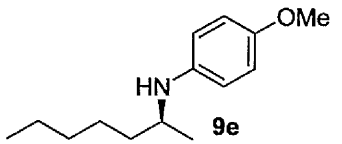
4-Methoxy-*N*-(pentan-2-yl)aniline.[20] The product (85 mg, 88% yield, 90% *ee*) was obtained according to the general procedure as a colourless oil from 2-pentanone (47 mg, 0.55 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.33-1.45 (m, 3H), 1.50-1.57 (m, 1H), 3.11 (brs, 1H), 3.38 (sextet, *J* = 6.3 Hz, 1H), 3.74 (s, 3H), 6.53-6.57 (m, 2H), 6.75-6.79 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 14.6, 19.8, 21.2, 39.9, 49.6, 56.2, 115.1, 115.4, 142.4, 152.2;
**HRMS** for $C_{12}H_{20}NO$ $[M+H]^+$: Calcd: 194.1545; Found: 194.1539;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 99:1, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 15.1 min (minor), $t_R$ = 15.8 min (major).




**9d**

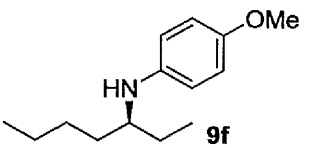
4-Methoxy-*N*-(hexan-2-yl)aniline.[37] The product (85 mg, 82% yield, 93% *ee*) was obtainedaccording to the general procedure as a colourless oil from 2-hexanone (55 mg, 0.55 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.90 (t, $J$ = 7.1 Hz, 3H), 1.15 (d, $J$ = 6.3 Hz, 3H), 1.30-1.42 (m, 5H), 1.53-1.59 (m, 1H), 3.36 (sextet, $J$ = 6.3 Hz, 1H), 3.74 (s, 3H), 6.53-6.57 (m, 2H), 6.75-6.79 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 14.5, 21.2, 23.2, 28.8, 37.4, 49.9, 56.3, 115.1, 115.4, 142.5, 152.2;
**HRMS** for $C_{13}H_{22}NO$ $[M+H]^+$: Calcd: 208.1701; Found: 208.1705;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 99:1, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 14.1 min (minor), $t_R$ = 14.7 min (major).



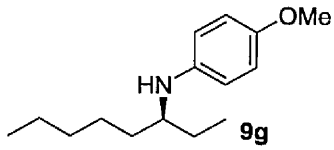
**9e**

*N*-(Heptan-2-yl)-4-methoxyaniline.[9,18] The product (87 mg, 79% yield, 91% *ee*) was obtainedaccording to the general procedure as a colourless oil from 2-heptanone (63 mg, 0.55 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** ($CDCl_3$, 400 MHz) δ 0.89 (t, $J$ = 6.8 Hz, 3H), 1.14 (d, $J$ = 6.3 Hz, 3H), 1.24-1.32 (m, 4H), 1.34-1.43 (m, 3H), 1.50-1.59 (m, 1H), 3.12 (brs, 1H), 3.32-3.39 (m, 1H),3.74 (s, 3H), 6.53-6.57 (m, 2H), 6.75-6.79 (m, 2H);
**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 14.4, 21.2, 23.1, 26.3, 32.3, 37.6, 50.0, 56.3, 115.1, 115.4, 142.4, 152.3;
**IR** (neat) 3656 (w), 2978 (s), 1512 (s), 1462 (m), 1381 (m), 1234 (s), 1153 (m), 818 (m) $cm^{-1}$;
**HRMS** for $C_{14}H_{24}NO$ $[M+H]^+$: Calcd: 222.1858; Found: 222.1852;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 99:1, flow rate 1.0 mL/min, λ = 254 nm): $t_R$ = 9.3 min (major), $t_R$ = 10.6 min (minor).



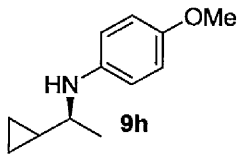
**9f**

*N*-(Heptan-3-yl)-4-methoxyaniline. The product (105 mg, 95% yield, 49% *ee*) was obtainedaccording to the general procedure as a colourless oil from 3-heptanone (63 mg, 0.55 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** ($CDCl_3$, 400 MHz) δ 0.89 (t, $J$ = 7.1 Hz, 3H), 0.91 (t, $J$ = 7.5 Hz, 3H), 1.26-1.59 (m, 8H), 3.18 (quintet, $J$ = 6.0 Hz, 1H), 3.74 (s, 3H), 6.52-6.56 (m, 2H), 6.74-6.78 (m, 2H);
**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 10.4, 14.5, 23.3, 27.5, 28.6, 34.4, 55.5, 56.3, 114.7, 115.4, 142.9, 151.9;
**IR** (neat) 3432 (w), 2981 (s), 2931 (m), 1601 (m), 1516 (m), 1458 (m), 1219 (m), 1030 (m), 733 (s) $cm^{-1}$;
**HRMS** for $C_{14}H_{24}NO$ $[M+H]^+$: Calcd: 222.1858; Found: 222.1850;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 99:1, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 14.0 min (major), $t_R$ = 15.8 min (minor).



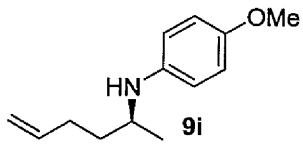

**9g**

4-Methoxy-*N*-(octan-3-yl)aniline. The product (94 mg, 80% yield, 71% *ee*) was obtainedaccording to the general procedure as a colourless oil from 3-octanone (71 mg, 0.55 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** ($CDCl_3$, 400 MHz) δ 0.86-0.93 (m, 6H), 1.27-1.59 (m, 10H), 3.14 (brs, 1H), 3.18 (quintet, $J$ = 5.9 Hz, 1H), 3.74 (s, 3H), 6.54 (d, $J$ = 8.8 Hz, 2H), 6.76 (d, $J$ = 8.8 Hz, 2H);
**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 10.4, 14.5, 23.1, 26.1, 27.5, 32.5, 34.7, 55.5, 56.3, 114.7, 115.3, 142.9, 151.9;
**HRMS** for $C_{15}H_{26}NO[M+H]^+$: Calcd: 236.2009; Found: 236.2006;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 99:1, flow rate 1.0 mL/min, λ = 254 nm): $t_R$ = 11.0 min (major), $t_R$ = 13.6 min (minor).




**9h**

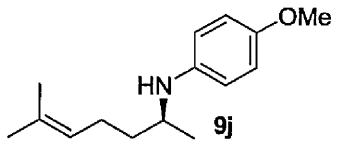
*N*-(1-Cyclopropylethyl)-4-methoxyaniline. The product (86 mg, 90% yield, 93% *ee*) was obtained according to the general procedure as a colourless oil from 1-cyclopropylethanone (46 mg, 0.55 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.21-0.31 (m, 2H), 0.43-0.52 (m, 2H), 0.86-0.95 (m, 1H), 1.20 (d, J = 6.3 Hz, 3H), 2.82-2.89 (m, 1H), 3.74 (s, 3H), 6.56-6.60 (m, 2H), 6.74-6.78 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 2.9, 3.6, 18.4, 20.7, 54.2, 56.2, 115.2, 115.5, 142.6, 152.3;
**HRMS** for $C_{12}H_{18}NO$ $[M+H]^+$: Calcd: 192.1388; Found: 192.1381;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 99:1, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 18.4 min (major), $t_R$ = 24.4 min (minor).




**9i**

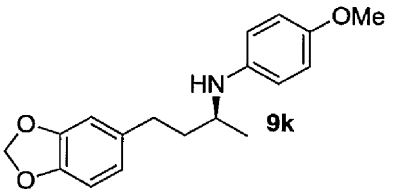
*N*-(Hex-5-en-2-yl)-4-methoxyaniline.[9,11] The product (82 mg, 80% yield, 92% *ee*) was obtainedaccording to the general procedure as a colourless oil from hex-5-en-2-one (54 mg, 0.55 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** ($CDCl_3$, 400 MHz) δ 1.15 (d, $J$ = 6.3 Hz, 3H), 1.38-1.47 (m, 1H), 1.54-1.63 (m, 1H), 2.05-2.11 (m, 2H), 3.10 (brs, 1H), 3.33 (sextet, $J$ = 6.3 Hz, 1H), 3.67 (s, 3H), 4.88-4.92 (m, 1H), 4.96 (dq, $J$ = 17.0, 1.7 Hz, 1H), 5.76 (ddt, $J$ = 17.0, 10.3, 6.7 Hz, 1H), 6.46-6.50 (m, 2H), 6.68-6.72 (m, 2H);
**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 21.2, 30.9, 36.7, 49.4, 56.2, 115.1, 115.2, 115.4, 138.9, 142.3, 152.3;

**HRMS** for $C_{13}H_{20}NO$ $[M+H]^+$: Calcd: 206.1545; Found: 206.1547;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 99:1, flow rate 1.0 mL/min, $\lambda$ = 254 nm): $t_R$ = 13.4 min (major), $t_R$ = 15.8 min (minor).



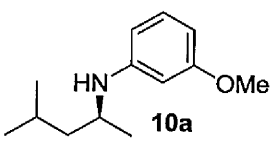
**9j**

4-Methoxy-*N*-(6-methylhept-5-en-2-yl)aniline.[21] The product (104 mg, 89% yield, 95% *ee*) was obtained according to the general procedure as a colourless oil from 6-methylhept-5-en-2-one (69 mg, 0.55 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.16 (d, $J$ = 6.3 Hz, 3H), 1.39-1.48 (m, 1H), 1.59 (s, 3H), 1.54-1.63 (m, 1H), 1.69 (d, $J$ = 0.8 Hz, 3H), 2.05-2.10 (m, 2H), 3.37 (sextet, $J$ = 6.3 Hz, 1H), 3.74 (s, 3H), 5.10-5.14 (m, 1H), 6.53-6.57 (m, 2H), 6.75-6.79 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 18.1, 21.2, 25.1, 26.1, 37.6, 49.5, 56.2, 115.1, 115.3, 124.5, 132.4, 142.5, 152.3;
**HRMS** for $C_{15}H_{24}NO$ $[M+H]^+$: Calcd: 234.1858; Found: 234.1865;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 99:1, flow rate 0.5 mL/min, $\lambda$ = 254 nm): $t_R$ = 21.6 min (major), $t_R$ = 26.9 min (minor).



**9k**

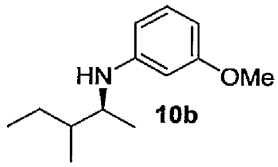
*N*-[4-(2H-1,3-Benzodioxol-5-yl)butan-2-yl]-4-methoxyaniline. The product (127 mg, 85% yield, 93% *ee*) was obtainedaccording to the general procedure as a colourless oil from 4-benzo[1,3]dioxol-5-yl-butan-2-one (106 mg, 0.55 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.18 (d, $J$ = 6.4 Hz, 3H), 1.65-1.74 (m, 1H), 1.78-1.87 (m, 1H), 2.64 (t, $J$ = 7.9 Hz, 2H), 3.36-3.41 (m, 1H), 3.75 (s, 3H), 5.92 (s, 2H), 6.53 (d, $J$ = 8.5 Hz, 2H), 6.62 (d, $J$ = 7.8 Hz, 1H), 6.67 (d, $J$ = 1.6 Hz, 1H), 6.72 (d, $J$ = 7.8 Hz, 1H), 6.75-6.77 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.3, 32.6, 39.5, 49.3, 56.2, 101.2, 108.6, 109.3, 115.2, 115.4, 121.6, 136.4, 142.1, 146.0, 148.0, 152.3;
**HRMS** for $C_{18}H_{22}NO_3$ $[M+H]^+$: Calcd: 300.1599; Found: 300.1590;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1 mL/min, $\lambda$ = 254 nm): $t_R$ = 28.7 min (major), $t_R$ = 38.6 min (minor).



**10a**

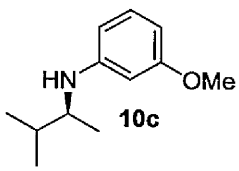
3-Methoxy-*N*-(4-methylpentan-2-yl)aniline. The product (75 mg, 72% yield, 80% *ee*) was obtained according the general procedure as a colourless oil from

4-methyl-2-pentanone (55 mg, 0.55 mmol) and *m*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.90 (d, $J$ = 6.6 Hz, 3H), 0.94 (d, $J$ = 6.6 Hz, 3H), 1.15 (d, $J$ = 6.8 Hz, 3H), 1.25 (dt, $J$ = 13.6, 6.8 Hz, 1H), 1.46 (dt, $J$ = 13.6, 6.9 Hz, 1H), 1.71-1.79 (m, 1H), 3.40 (brs, 1H), 3.46-3.54 (m, 1H), 3.76 (s, 3H), 6.13 (t, $J$ = 2.2 Hz, 1H), 6.21 (dd, $J$ = 8.1, 2.2 Hz, 2H), 7.06 (t, $J$ = 8.1 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.5, 23.0, 23.4, 25.5, 47.0, 47.3, 55.5, 99.3, 102.2, 106.7, 130.4, 149.5, 161.3;
**HRMS** for $C_{13}H_{22}NO$ $[M+H]^+$: Calcd: 208.1701; Found: 208.1711;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 19.9 min (minor), $t_R$ = 21.9 min (major).



**10b**

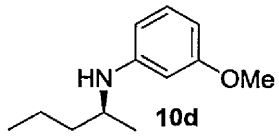
3-Methoxy-*N*-(3-methylpentan-2-yl)aniline (**10b**). Mixture of diastereoisomers 54:46.The product (85 mg, 82% yield, 96% *ee*) was obtained according the general procedure as a colourless oil from (+/-)-3-methylpentan-2-one (55 mg, 0.55 mmol) and *m*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.86 (d, $J$ = 6.8 Hz, 1.5H), 0.89 (t, $J$ = 7.4 Hz, 1.5H), 0.82-0.96 (m, 3H), 1.06 (d, $J$ = 6.5 Hz, 1.5H), 1.10 (d, $J$ = 6.5 Hz, 1.5H), 1.13-1.23 (m, 1H), 1.44-1.65 (m, 2H), 3.40-3.45 (m, 1H), 3.53 (brs, 1H), 3.76 (s, 3H), 6.13 (t, $J$ = 2.2 Hz, 1H), 6.18-6.23 (m, 2H), 7.03-7.07 (m, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 12.3(6), 12.4(3), 14.2, 15.7, 16.3, 17.7, 25.3, 26.9, 38.9, 39.6, 52.1, 52.7, 55.5, 99.2, 99.3, 101.9, 102.0, 106.6,(3), 106.6(7), 130.4, 149.5, 149.7, 161.3;
**HRMS** for $C_{13}H_{22}NO$ $[M+H]^+$: Calcd: 208.1701; Found: 208.1700;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 99.5:0.5, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 46.7 min (d1, major), $t_R$ = 50.3 min (d2, major), $t_R$ = 55.6 (d1, minor), $t_R$ = 58.2 (d2, minor).



**10c**

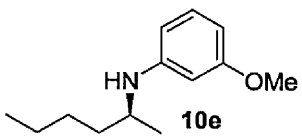
3-Methoxy-*N*-(3-methylbutan-2-yl)aniline. The product (83 mg, 86% yield, 90% *ee*) was obtained according the general procedure as a colourless oil from 3-methylbutan-2-one (47 mg, 0.55 mmol) and *m*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.90 (d, $J$ = 6.8 Hz, 3H), 0.96 (d, $J$ = 8.0 Hz, 3H), 1.09 (d, $J$ = 6.5 Hz, 3H), 1.80-1.88 (m, 1H), 3.28-3.42 (m, 1H), 3.52 (brs, 1H), 3.76 (s, 3H), 6.13 (t, $J$ = 2.3 Hz, 1H), 6.18-6.23 (m, 2H), 7.05 (t, $J$ = 8.1 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 17.0, 17.9, 19.6, 32.6, 53.8, 55.5, 99.3, 102.0, 106.7, 130.4, 149.6, 161.3;
**HRMS** for $C_{12}H_{20}NO$ $[M+H]^+$: Calcd: 194.1539; Found: 194.1541;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 10.9 min (minor), $t_R$ = 12.9 min (major).



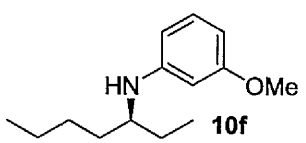
**10d**

3-Methoxy-*N*-(pentan-2-yl)aniline. The product (74 mg, 77% yield, 91% *ee*) was obtained according the general procedure as a colourless oil from 2-pentanone (47 mg, 0.55 mmol) and *m*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.92 (t, $J$ = 7.1 Hz, 3H), 1.16 (d, $J$ = 6.3 Hz, 3H), 1.36-1.43 (m, 3H), 1.52-1.57 (m, 1H), 3.41-3.48 (m, 2H), 3.77 (s, 3H), 6.13 (t, $J$ = 2.3 Hz, 1H), 6.19 (ddd, $J$ = 8.1, 2.3, 0.8 Hz, 1H), 6.23 (ddd, $J$ = 8.1, 2.3, 0.8 Hz, 1H), 7.06 (t, $J$ = 8.1 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 14.5, 19.7, 21.2, 39.8, 48.7, 55.5, 99.5, 102.3, 106.8, 130.4, 149.4, 161.3;
**HRMS** for $C_{13}H_{22}NO$ $[M+H]^+$: Calcd: 194.1539; Found: 194.1540;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 14.4 min (minor), $t_R$ = 16.0 min (major).



**10e**

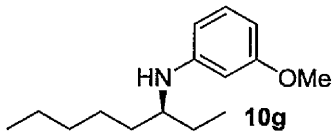
*N*-(Hexan-2-yl)-3-methoxyaniline.[22] The product (88 mg, 85% yield, 92% *ee*) was obtained according the general procedure as a colourless oil from 2-hexanone (55 mg, 0.55 mmol) and *m*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.90 (t, $J$ = 7.1 Hz, 3H), 1.16 (d, $J$ = 6.3 Hz, 3H), 1.30-1.45 (m, 5H), 1.52-1.58 (m, 1H), 3.43 (sextet, $J$ = 6.3 Hz, 1H), 3.46 (brs, 1H), 3.77 (s, 3H), 6.13 (t, $J$ = 2.3 Hz, 1H), 6.18-6.24 (m, 2H), 7.06 (t, $J$ = 8.1 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 14.5, 21.2, 23.2, 28.8, 37.3, 49.0, 55.5, 99.5, 102.3, 106.8, 130.4, 149.3, 161.3;
**HRMS** for $C_{13}H_{22}NO$ $[M+H]^+$: Calcd: 208.1696; Found: 208.1696;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 13.5 min (minor), $t_R$ = 15.5 min (major).



**10f**

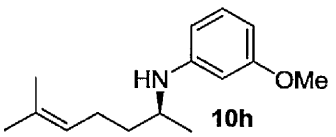
*N*-(Heptan-3-yl)-3-methoxyaniline. The product (90 mg, 81% yield, 61% *ee*) was obtained according the general procedure as a colourless oil from 3-heptanone (63 mg, 0.55 mmol) and *m*-anisidine (62 mg, 0.5 mmol) in 20 h;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.89 (t, $J$ = 7.0 Hz, 3H), 0.91 (t, $J$ = 7.4 Hz, 3H), 1.24-1.63 (m, 8H), 3.25 (quintet, $J$ = 6.0 Hz, 1H), 3.45 (brs, 1H), 3.77 (s, 3H), 6.12 (t, $J$ = 2.2 Hz, 1H), 6.17-6.22 (m, 2H), 7.05 (t, $J$ = 8.1 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 10.5, 14.5, 23.3, 27.7, 28.6, 34.5, 54.5, 55.5, 99.1, 101.8, 106.5, 130.4, 150.0, 161.3;
**HRMS** for $C_{14}H_{24}NO[M+H]^+$: Calcd: 222.1852; Found: 222.1851;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 12.6 min (minor), $t_R$ = 15.9 min (major).



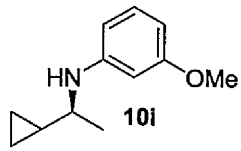
**10g**

3-Methoxy-*N*-(octan-3-yl)aniline. The product (98 mg, 83% yield, 64% *ee*) was obtained according the general procedure as a colourless oil from 3-octanone (71 mg, 0.55 mmol) and *m*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.87 (t, $J$ = 7.0 Hz, 3H), 0.91 (t, $J$ = 7.5 Hz, 3H), 1.25-1.61 (m, 10H), 3.22-3.28 (m, 1H), 3.44 (brs, 1H), 3.77 (s, 3H), 6.12 (t, $J$ = 2.2 Hz, 1H), 6.17-6.22 (m, 2H), 7.05 (t, $J$ = 8.1 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 10.5, 14.5, 23.1, 26.1, 27.7, 32.4, 34.8, 54.5, 55.5, 99.1, 101.8, 106.5, 130.4, 150.0, 161.3;
**HRMS** for $C_{15}H_{26}NO[M+H]^+$: Calcd: 236.2009; Found: 236.2008;
**HPLC** (Chiralcel OJ, hexane:isopropanol = 99.5:0.5, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 21.2 min (major), $t_R$ = 25.2 min (minor).



**10h**

1-(2,6-Dimethylhept-5-enyl)-3-methoxybenzene.[22] The product (78 mg, 67% yield, 82% *ee*) was obtained according the general procedure as a colourless oil from 6-methylhept-5-en-2-one (69 mg, 0.55 mmol) and *m*-anisidine (62 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.17 (d, $J$ = 6.3 Hz, 3H), 1.43-1.50 (m, 1H), 1.55-1.64 (m, 1H), 1.59 (s, 3H), 1.69 (d, $J$ = 0.8 Hz, 3H), 2.07 (q, $J$ = 7.4 Hz, 2H), 3.44 (sextet, $J$ = 6.3 Hz, 1H), 3.51 (brs, 1H), 3.76 (s, 3H), 5.10-5.14 (m, 1H), 6.13 (t, $J$ = 2.2 Hz, 1H), 6.19 (dd, $J$ = 8.0, 2.2 Hz, 1H), 6.23 (dd, $J$ = 8.0, 2.2 Hz, 1H), 7.05 (t, $J$ = 8.0 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 18.1, 21.2, 25.1, 26.1, 37.5, 48.6, 55.5, 99.4, 102.3, 106.8, 124.4, 130.4, 132.5, 149.4, 161.3;
**HRMS** for $C_{15}H_{24}NO[M+H]^+$: Calcd: 234.1858; Found: 234.1857;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 20.5 min (minor), $t_R$ = 21.6 min (major).




**10i**

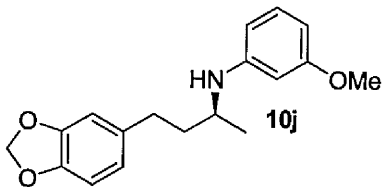
*N*-(1-Cyclopropylethyl)-3-methoxyaniline.[22] The product (59 mg, 62% yield, 82% *ee*) was obtained according the general procedure as a colourless oil from 1-cyclopropylethanone (46 mg, 0.55 mmol) and *m*-anisidine (62 mg, 0.5 mmol) in 20 h;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.23-0.34 (m, 2H), 0.43-0.53 (m, 2H), 0.89-0.96 (m, 1H), 1.22 (d, $J$=6.3 Hz, 3H), 2.92-2.99 (m, 1H), 3.76 (s, 3H), 6.15 (t, $J$= 2.2 Hz, 1H), 6.20-6.25 (m, 2H), 7.05 (t, $J$= 8.1 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 3.0, 3.5, 18.2, 20.6, 53.0, 55.5, 99.6, 102.5, 106.9, 130.3, 149.5, 161.2;

**HRMS** for $C_{12}H_{18}NO$ $[M+H]^+$: Calcd: 192.1383; Found: 192.1386;

**HPLC** (Chiralcel OD-H, hexane:isopropanol = 99.5:0.5, flow rate 1 mL/min, λ = 254 nm): $t_R$ = 37.0 min (major), $t_R$ = 38.0 min (minor).




**10j**

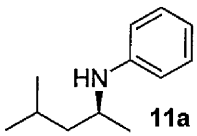
*N*-(4-(Benzo[d][1,3]dioxol-5-yl)butan-2-yl)-3-methoxyaniline. The product (120 mg, 80% yield, 91% *ee*) was obtained according the general procedure as a colourless oil from 4-benzo[1,3]dioxol-5-yl-butan-2-one (106 mg, 0.55 mmol) and *m*-anisidine (62 mg, 0.5 mmol) in 20 h;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.19 (d, $J$ = 6.3 Hz, 3H), 1.66-1.75 (m, 1H), 1.77-1.86 (m, 1H), 2.63 (t, $J$ = 7.8 Hz, 2H), 3.45 (sextet, $J$ = 6.3 Hz, 1H), 5.91 (s, 2H), 6.09 (t, $J$ = 2.2 Hz, 1H), 6.14-6.17 (m, 1H), 6.22-6.25 (m, 1H), 6.62 (dd, $J$ = 7.8, 1.6 Hz, 1H), 6.67 (d, $J$ = 1.6 Hz, 1H), 6.72 (d, $J$ = 7.8 Hz, 1H), 7.05 (t, $J$ = 8.1 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.3, 32.6, 39.5, 48.2, 55.5, 99.4, 101.2, 102.4, 106.7, 108.6, 109.3, 121.5, 130.4, 136.2, 146.0, 148.0, 149.3, 161.3;

**HRMS** for $C_{18}H_{22}NO_3$ $[M+H]^+$: Calcd: 300.1588; Found: 300.1600;

**HPLC** (Chiralcel OD-H, hexane:isopropanol = 90:10 flow rate 1 mL/min, λ = 254 nm): $t_R$ = 25.5 min (major), $t_R$ = 29.2 min (minor).

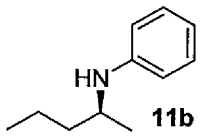



**11a**

*N*-(4-Methylpentan-2-yl)aniline.[18,38] The product (71 mg, 80% yield, 88% *ee*) was obtained according to the general procedure as a colourless oil from 4-methylpentan-2-one (55 mg, 0.55 mmol) and aniline (47 mg, 0.5 mmol) in 20 h;

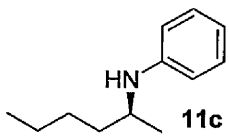
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.91 (d, $J$= 6.6 Hz, 3H), 0.94 (d, $J$ = 6.6 Hz, 3H), 1.16 (d, $J$= 6.3 Hz, 3H), 1.26 (dt, $J$= 13.7, 6.9 Hz, 1H), 1.47 (dt, $J$= 13.7,

6.9 Hz, 1H), 1.70-1.80 (m, 1H), 3.39 (brs, 1H), 3.47-3.57 (m, 1H), 6.56-6.59 (m, 2H), 6.65 (tt, J = 7.3, 1.0 Hz, 1H), 7.13-7.20 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.5, 23.1, 23.4, 25.5, 46.9, 47.4, 113.5, 117.2, 129.8, 148.2;
**HRMS** for $C_{12}H_{20}N$ $[M+H]^+$: Calcd: 178.1596; Found: 178.1590;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 99.5:0.5, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 7.7 min (minor), $t_R$ = 8.6 min (major).



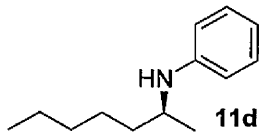

**11b**

*N*-(Pentan-2-yl)aniline.[39] The product (75 mg, 92% yield, 94% *ee*) was obtainedaccording to the general procedure as a colourless oil from 2-pentanone (47 mg, 0.55 mmol) and aniline (47 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 6.2 Hz, 3H), 1.35-1.46 (m, 3H), 1.50-1.60 (m, 1H), 3.45 (brs, 1H), 3.47 (sextet, *J* = 6.2 Hz, 1H), 6.55-6.58 (m, 2H), 6.65 (tt, *J* = 7.3, 1.0 Hz, 1H), 7.13-7.20 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 14.5, 19.7, 21.2, 39.9, 48.6, 113.5, 117.1, 129.7, 148.3;
**HRMS** for $C_{11}H_{18}N$ $[M+H]^+$: Calcd: 164.1439; Found: 164.1440;
**HPLC** (Chiralcel OJ, hexane:isopropanol = 99.5:0.5, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 28.8 min (major), $t_R$ = 34.8 min (minor).The *ee* was determined by weighing the HPLC peaks, as the peak corresponding to the minor enantiomer was too small and wide to be integrated.



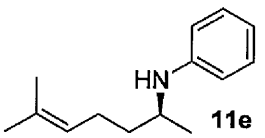

**11c**

*N*-(hexan-2-yl)aniline.[40] The product (75 mg, 85% yield, 95% *ee*) was obtainedaccording to the general procedure as a colourless oil from 2-hexanone (55 mg, 0.55 mmol) and aniline (47 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.28-1.47 (m, 5H), 1.53-1.56 (m, 1H), 3.41-3.48 (m, 2H), 6.55-6.58 (m, 2H), 6.65 (tt, *J* = 7.3, 1.0 Hz, 1H), 7.13-7.18 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 14.5, 21.2, 23.2, 28.8, 37.4, 48.8, 113.5, 117.1, 129.7, 148.1;
**HRMS** for $C_{12}H_{20}N$ $[M+H]^+$: Calcd: 178.1596; Found: 178.1590;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 99.5:0.5, flow rate 0.25 mL/min, λ = 254 nm): $t_R$ = 18.2 min (minor), $t_R$ = 19.1 min (major).



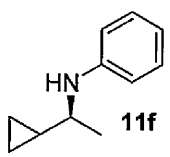

**11d**

*N*-(Heptan-2-yl)aniline.[24,41] The product (79 mg, 83% yield, 92% *ee*) was obtainedaccording to the general procedure as a colourless oil from 2-heptanone (63 mg, 0.55 mmol) and aniline (47 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, $J$ = 7.0 Hz, 3H), 1.17 (d, $J$ = 6.3 Hz, 3H), 1.26-1.46 (m, 7H), 1.53-1.59 (m, 1H), 3.41 (brs, 1H), 3.44 (sextet, $J$ = 6.3 Hz, 1H), 6.55-6.58 (m, 2H), 6.65 (tt, $J$ = 7.3, 1.0 Hz, 1H), 7.13-7.18 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 14.4, 21.2, 23.1, 26.2, 32.3, 37.6, 48.9, 113.5, 117.1, 129.7, 148.3;
**HRMS** for $C_{13}H_{22}N$ $[M+H]^+$: Calcd: 192.1752; Found: 192.1754;
**HPLC** (Chiralcel OB-H, hexane:isopropanol = 99.5:0.5, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 8.8 min (minor), $t_R$ = 9.7 min (major).




**11e**

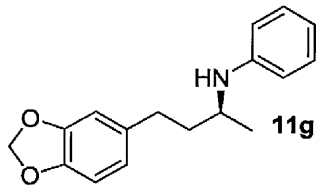
*N*-(6-Methylhept-5-en-2-yl)aniline. The product (93 mg, 91% yield, 91% *ee*) was obtainedaccording to the general procedure as a colourless oil from 6-methylhept-5-en-2-one (69 mg, 0.55 mmol) and aniline (47 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.17 (d, $J$ = 6.3 Hz, 3H), 1.42-1.51 (m, 1H), 1.59 (s, 3H), 1.55-1.64 (m, 1H), 1.69 (d, $J$ = 1.0 Hz, 3H), 2.08 (q, $J$ = 7.2 Hz, 2H), 3.43 (brs, 1H), 3.46 (sextet, $J$ = 6.3 Hz, 1H), 5.10-5.14 (m, 1H), 6.55-6.58 (m, 2H), 6.65 (tt, $J$ = 7.4, 1.0 Hz, 1H), 7.13-7.17 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 18.1, 21.2, 25.1, 26.1, 37.6, 48.5, 113.5, 117.2, 124.4, 129.7, 132.4, 148.2;
**HRMS** for $C_{14}H_{22}N$ $[M+H]^+$: Calcd: 204.1752; Found: 204.1749;
**HPLC** (Chiralcel OJ, hexane:isopropanol = 99:1, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 15.3 min (major), $t_R$ = 19.4 min (minor).




**11f**

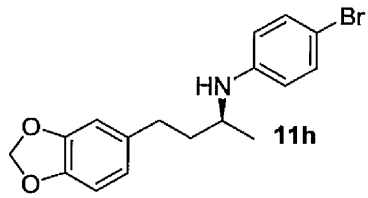
*N*-(1-Cyclopropylethyl)aniline. The product (73 mg, 91% yield, 92% *ee*) was obtainedaccording to the general procedure as a colourless oil from 1-cyclopropylethanone (46 mg, 0.55 mmol) and aniline (47 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.22-0.33 (m, 2H), 0.44-0.53 (m, 2H) 0.88-0.97 (m, 1H), 1.22 (d, $J$ = 6.5 Hz, 3H), 2.97 (quintet, $J$ = 6.5 Hz, 1H), 3.66 (brs, 1H), 6.57-6.60 (m, 2H), 6.66 (tt, $J$ = 7.3, 1.0 Hz, 1H), 7.13-7.18 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 3.0, 3.5, 18.3, 20.6, 52.9, 113.6, 117.3, 129.6, 148.3;

**IR** (neat) 3660 (w), 2977 (m), 2888 (w), 1601 (m), 1504 (m), 1315 (w), 748 (s), 690 (m) $cm^{-1}$;
**HRMS** for $C_{11}H_{16}N$ $[M+H]^+$: Calcd: 162.1283; Found: 162.1286;
**HPLC** (Chiralcel OJ, hexane:isopropanol = 99.5:0.5, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 32.4 min (major), $t_R$ = 37.3 min (minor). The *ee* was determined by weighing the HPLC peaks, as the peak corresponding to the minor enantiomer was too small and wide to be integrated.



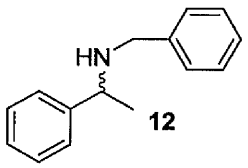
**11g**

*N*-[4-(2H-1,3-Benzodioxol-5-yl)butan-2-yl]aniline. The product (128 mg, 95% yield, 91% *ee*) was obtained according to the general procedure as a colourless oil from 4-(benzo[1,3]dioxol-5-yl-butan-2-one (106 mg, 0.55 mmol) and aniline (47 mg, 0.5 mmol) in 20 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.3 Hz, 3H), 1.67-1.76 (m, 1H), 1.78-1.87 (m, 1H), 2.64 (t, *J* = 7.8 Hz, 2H), 3.42 (brs, 1H), 3.47 (sextet, *J* = 6.3 Hz, 1H), 5.91 (s, 2H), 6.52-6.55 (m, 2H), 6.62 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.64-6.68 (m, 2H), 6.72 (d, *J* = 7.9 Hz, 1H), 7.12-7.17 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.3, 32.6, 39.5, 48.2, 101.2, 108.6, 109.3, 113.6, 117.4, 121.5, 129.7, 136.2, 146.0, 147.9, 148.0;
**HRMS** for $C_{17}H_{20}NO_2$ $[M+H]^+$: Calcd: 270.1494; Found: 270.1503;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1 mL/min, λ = 254 nm): $t_R$ = 22.4 min (major), $t_R$ = 24.8 min (minor).



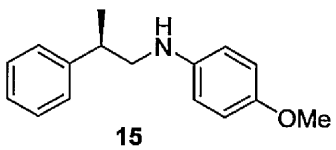
**11h**

*N*-(4-(Benzo[d][1,3]dioxol-5-yl)butan-2-yl)-4-bromoaniline. The product (122 mg, 70% yield, 84% *ee*) was obtained according the general procedure as a colourless oil from 4-(benzo[1,3]dioxol-5-yl-butan-2-one (106 mg, 0.55 mmol) and *p*-bromoaniline (86 mg, 0.5 mmol) in 30 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.1 Hz, 3H), 1.66-1.84 (m, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 3.36-3.43 (m, 1H), 3.43 (brs, 1H), 5.92 (s, 2H), 6.39 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 7.8 Hz, 1H), 6.65 (s, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.1, 32.5, 39.3, 48.2, 101.2, 108.6, 108.7, 109.3, 115.1, 121.5, 132.4, 136.0, 146.1, 146.9, 148.0;
**HRMS** for $C_{17}H_{19}{}^{79}BrNO_2$ $[M+H]^+$: Calcd: 348.0599; Found: 348.0592;
**HPLC** (Chiralcel OJ, hexane:isopropanol = 90:10, flow rate 1 mL/min, λ = 254 nm): $t_R$ = 46.8 min (major), $t_R$ = 65.6 min (minor).




**12**

*N*-Benzyl-1-phenylethanamine.[30] The product (95 mg, 90% yield) was obtained according to the general procedure as a colourless oil, with catalyst **6c** in TFE, from acetophenone (66 mg, 0.55 mmol) and benzylamine (53 mg, 0.5 mmol);
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.29 (d, $J$ = 6.6 Hz, 3H), 3.51 (d, A of AB, $J_{AB}$ = 13.1 Hz, 1H), 3.58 (d, B of AB, $J_{AB}$ = 13.1 Hz, 1H), 3.73 (q, $J$ = 6.6 Hz, 1H), 7.13-7.27 (m, 10H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 23.4, 50.6, 56.4, 125.7, 125.8, 125.9, 127.1, 127.3, 127.4, 139.5, 144.4;
**HRMS** for $C_{15}H_{18}N$ $[M+H]^+$: Calcd: 212.1434; Found: 212.1430;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 99.9:0.1, flow rate 1 mL/min, λ = 220 nm): $t_R$ = 16.6 min, $t_R$ = 20.5 min.




**15**

4-Methoxy-*N*-(2-phenylpropyl)aniline.[14] The product (111 mg, 92% yield, 53% *ee*) was obtained according to the general procedure as a colourless oil;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.32 (d, J = 7.0 Hz, 3H), 3.00-3.08 (m, 1H), 3.19 (dd, A of ABX, $J_{AB}$ = 12.2 Hz, $J_{AX}$ = 8.3 Hz, 1H), 3.30 (dd, B of ABX, $J_{AB}$ = 12.2 Hz, $J_{BX}$ = 6.1 Hz, 1H), 3.74 (s, 3H), 6.52-6.56 (m, 2H), 6.74-6.77 (m, 2H), 7.21-7.25 (m, 3H), 7.30-7.35 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 19.8, 39.2, 52.0, 55.8, 114.4, 114.9, 126.6, 127.3, 128.7, 142.4, 144.6, 152.1;
**HRMS** for $C_{16}H_{20}NO$ $[M+H]^+$: Calcd: 242.1539; Found: 242.1537;
**HPLC** (Chiralcel OJ, hexane :isopropanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 19.6 min (minor), $t_R$ = 23.1 min (major).

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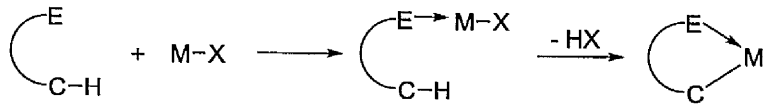
# Chapter 3

# Achiral Cyclometallated Complexes for Imine Hydrogenation

## 3.1 Introduction

The term *Cyclometallation Reaction* was introduced by Trofimenko in 1973 when he studied the formation of Pd-C bond with a series of Pd complexes and derivatives of benzylamine.[1] It is defined as "the intramolecular reaction of a transition metal complex with an organic ligand where a metal-carbon σ bond is formed".[2] The reaction may occur as follows. The ligand coordinates to the metal, followed by cyclometallation. The metal-carbon formation is facilitated by the presence of a good leaving basic group in the complex, which combines with the hydrogen atom that has been eliminated from the metallated carbon atom (Scheme 3.1).




**Scheme 3.1**: General scheme of cyclometallation reaction.[2] E: donor group; X: leaving group.

A typical cyclometallation reaction refers to the coordination of a heteroatom to a metal centre. C-H activation then takes place, giving rise to a covalent metal-carbon bond. The dative bond is normally derived from heteroatoms such as nitrogen in the ligand. Five-membered rings are usually regioselectively formed, as it is more stable than four- and six-membered rings.[3]

Although cyclometallated reactions were not "baptised" until 1973, the first example of a cyclometallated reaction was reported by Cope and Siekman in 1965.[4] They synthesised cyclometallated Pt and Pd dimer complexes from the reaction of azobenzene with $K_2PtCl_2$ or $PdCl_2$, respectively (Figure 3.1). Since then, a wide variety of these organotransition metal compounds have been synthesised by cyclometallation. They can be highly active in catalytic reactions and have presented catalytic activity for a number of transformations, such as reduction,[5-8] dehydrogenation[9-12] and cross-coupling reactions.[13-16]

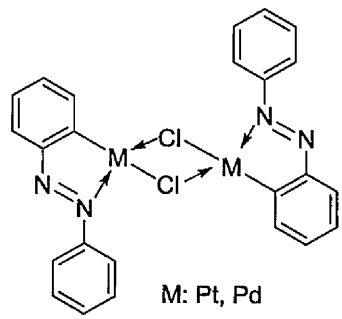
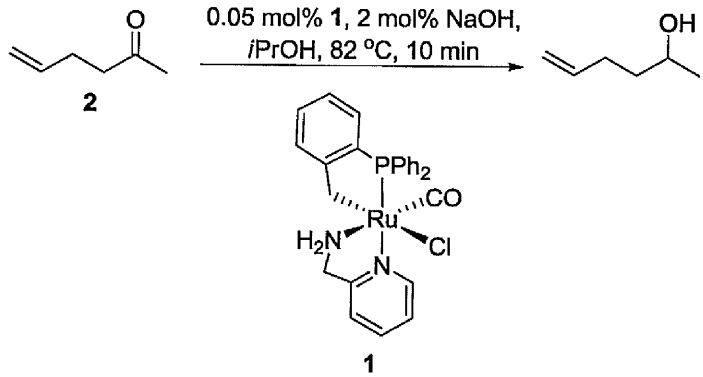



**Figure 3.1**: First example of synthesis of cyclometallated complexes.

The use of cyclometallated complexes as catalysts for the reduction of unsaturated functional groups has also been demonstrated. Baratta and co-workers reported the first application of a cyclometallated metal complex in catalytic transfer hydrogenation.[5] They reported the synthesis of ruthenium complex **1** containing a simple P,C ligand and a 2-(aminomethyl)pyridine ligand. **1** was found to be very active for the reduction of ketones with TOF up to 63,000 $h^{-1}$ (Scheme 3.2). The reaction takes place at 82 °C in 2-propanol, which acts as both the solvent and hydrogen source. It is noteworthy that this catalyst is chemoselective for ketones over olefins. Thus, ketone **2** is

selectively converted into its corresponding alcohol without reduction or isomerisation of the C=C double bond (Scheme 3.2).




**Scheme 3.2**: First application of a cyclometallated metal complex for transfer hydrogenation.

Subsequently, Ramesh *et al.* studied the TH of benzophenone with a series of cyclometallated ruthenium(III) complexes containing 2-(arylazo)phenol ligands **3** (Figure 3.2), halide and triphenylphosphine.[6] The reduction takes places at 82 °C with 1 mol% catalyst in the presence of 2.5 mol% KOH in *i*PrOH. Although this type of complex catalyses the reduction of benzophenone with high conversion, its activity did not surpass that of the complex previously reported by Baratta.

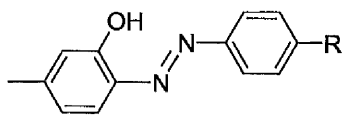
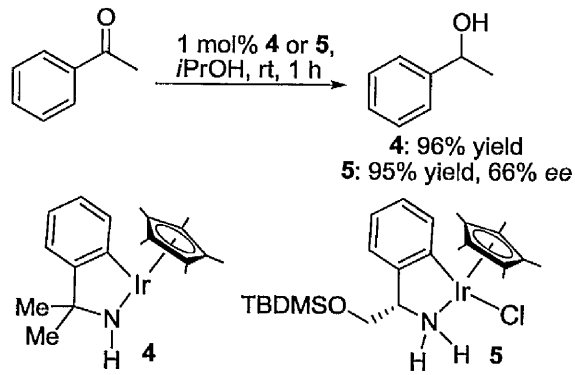



**Figure 3.2**: 2-(Arylazo)phenol ligand.

Ikariya and co-workers also reported the application of a cyclometallated complex to catalytic TH of ketones.[7] They synthesised a series of 16e amido complexes **4**, containing the metal/NH bifunctionality. These complexes were readily and reversibly converted into the corresponding metal hydride. Due to this reversibility they were successfully applied to the TH of acetophenone with *i*PrOH or formic acid (Scheme 3.3). Acetophenone was fully reduced after 1 hour with 1 mol% catalyst loading. Therefore, this catalyst was shown to be more effective than the classical Ir-Ts-diamine. Asymmetric reduction was also attempted with catalyst **5**. Although only moderate enantioselectivities were obtained, the tunability of the ligands makes improvement in selectivity very promising.




**Scheme 3.3**: Asymmetric transfer hydrogenation of acetophenone with Ir-metallacycle catalysts.

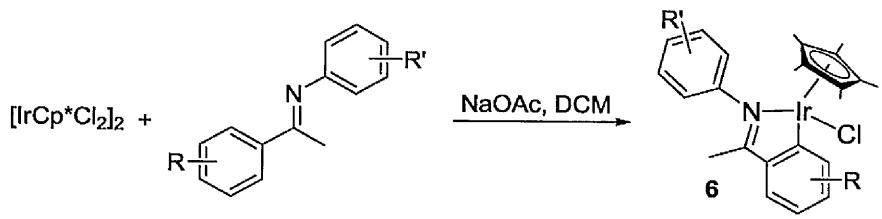
Although still in their infancy, cyclometallated complexes have showed to be effective for the reduction of polar C=O bonds. Furthermore, the presence of a robust cyclometallated metal-carbon bond apparently allows the formation of a long-lived catalytic species.[6] The combination of both features prompted us to apply this type of complex for the reduction of C=N double bonds. It would

be very desirable, from an industrial point of view, to design a highly active as well as stable catalyst for the reduction of imines.

## 3.2 Results and discussion

### 3.2.1 Optimisation of conditions

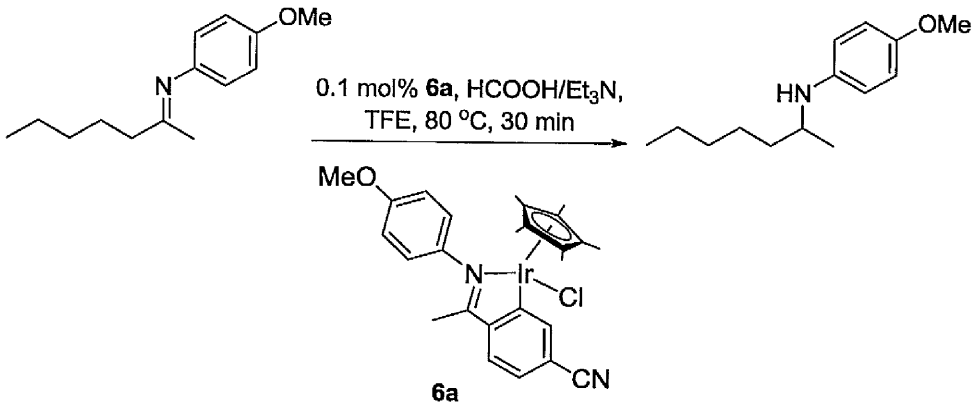
A series of cyclometallated Ir-imine complexes were synthesised from $[IrCp^*Cl_2]_2$ and aryl imines, following a procedure developed by Davies and co-workers (Scheme 3.4).[17] Mechanistic studies developed by Jones *et al.* suggest that the cyclometallation follows an electrophilic C-H activation mechanism.[18] The proposed mechanism involves the formation of cationic 16e species $[IrCp^*(OAc)]^+$, followed by imine coordination and C-H cleavage. The rate-determining step is considered to be the C-H cleavage.




**Scheme 3.4**: Synthesis of cyclometallated Ir-imine complexes.

Recently, our group applied this type of Ir-cyclometallated complexes for imine reduction and reductive amination under TH conditions.[8] Although non-chiral, this type of complexes shows high chemoselectivity and activity for the reduction of C=N bond, with initial TOF up to $1.9 \times 10^{-4}$ $h^{-1}$ (Scheme 3.5). Moreover, they are effective for a wide range of substrates, including derivatives of aromatic and aliphatic ketones and amines. In addition, these

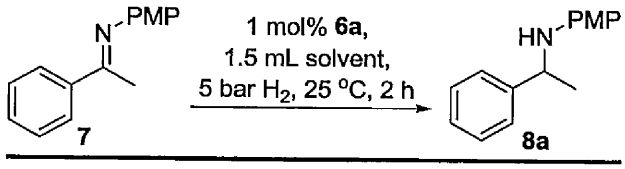
complexes are very easy to synthesise and are air-stable. These features prompted us to investigate their application for imine reduction under hydrogenation conditions. The use of $H_2$ as the hydrogen source would provide a much cleaner, more scalable reaction.




**Scheme 3.5:** Ir-metallacycle complex for TH of imines.[8]

The initial hydrogenation experiments were carried out on substrate **7** at room temperature under 5 bar of $H_2$ for 2 hours. Firstly, the activity of catalyst **6a** was compared in a series of solvents, which shows that TFE is the solvent of choice (Table 3.1). It is understood that the active catalytic system is the cationic 16e species, formed after removal of the chloride ligand. TFE has high polarity and low nucleophilicity.[19] Therefore, it helps the dissociation and solvation of the chloride ion, while having minimal interaction with the cationic 16e species.

**Table 3.1**: Screening of solvents for the hydrogenation of 7.



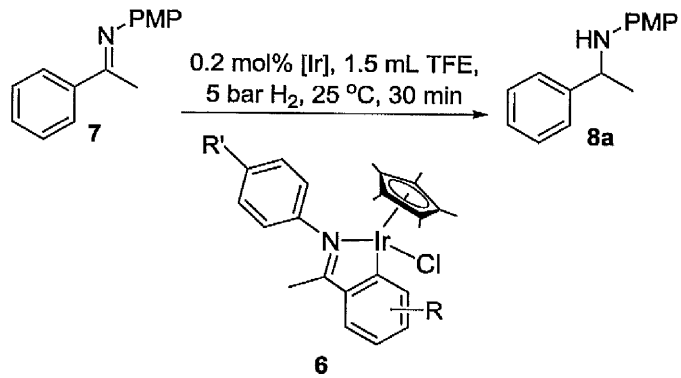

| Entry | Solvent | Conversion (%)[a] |
|---|---|---|
| 1 | TFE | > 99 |
| 2 | MeOH | 7 |
| 3 | EtOH | 2 |
| 4 | DMSO | N.R. |
| 5 | DMF | N.R. |
| 6 | DCM | N.R. |
| 7 | Toluene | N.R. |

[a] Determined by $^1$H NMR.

One of the main features of these cyclometallated complexes is the modular nature of the ligand, as different substituents can be added in either the aryl ketone ring or the *N*-aryl ring. Therefore, the electronic effects of different substituents were then studied for catalytic activity (Table 3.2). The reaction with 0.1 mol% of $[IrCp^*Cl_2]_2$, a precursor for this type of cyclometallated complexes, was first run. The substrate could act as a ligand, forming the cyclometallated complex *in situ*. However, no reaction was observed (Entry 1). In comparison, 51% conversion was observed when the catalyst had been previously synthesised (entry 4), suggesting that the reaction conditions do not promote the cyclometallation and it is necessary to pre-prepare the catalyst. When changing the *para*-substituents at the ketone ring, electron-deficient groups clearly enhance the activity (entries 2-6). However, the position of the substituent has a significant effect on the catalyst: the nitro group at the *meta*-

position led to a much lower conversion (entry 7 *vs* 8). The *p*-MeO group in the aniline ring proves to be important for good activity as well (entry 6 *vs* 9). This substituent makes the nitrogen atom more electron-donating, therefore a better Lewis base (higher HOMO), favouring coordination of the nitrogen to the metal centre. The best result was obtained with complex **6f**, with 87% conversion being observed after 30 minutes, at 0.2 mol% catalyst loading, room temperature and under 5 bar $H_2$.

**Table 3.2**: Ligand effect on hydrogenation of 7.

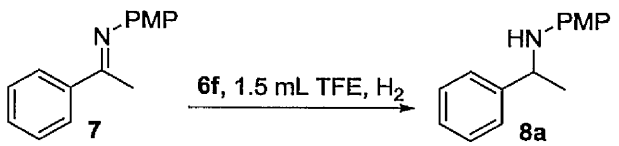



| Entry | [Ir] | R | R' | Conv. (%)[a] |
|---|---|---|---|---|
| 1 | $[IrCp^*Cl_2]_2$ | - | - | 1 |
| 2 | **6b** | *p*-*i*Bu | OMe | 9 |
| 3 | **6c** | *p*-OMe | OMe | 21 |
| 4 | **6d** | H | OMe | 51 |
| 5 | **6e** | *p*-Br | OMe | 54 |
| 6 | **6a** | *p*-CN | OMe | 74 |
| 7 | **6f** | *p*-$NO_2$ | OMe | 87 |
| 8 | **6g/6h**[b] | *m*-$NO_2$ | OMe | 26 |
| 9 | **6i** | *p*-CN | H | 37 |

[a]Determined by $^1$H NMR. [b]Mixture of regioisomers: **6g**:**6h** 7:1, see analytical data.

Having identified the best ligand, our attention turned to optimisation of the reaction conditions to enhance the activity. The increase of the hydrogen pressure had a positive effect on the activity, as can be seen from Table 3.3 (entry 1 *vs* 2 and 3; entry 4 *vs* 5). While 76% conversion was obtained after 15 minutes under 5 bar $H_2$ (entry 1), a similar conversion (65%) was obtained after only 5 minutes under 20 bar $H_2$ (entry 5). An increase in temperature also led to higher activity, suggesting that the catalyst is stable at high temperatures. Therefore, the optimal conditions chosen for examining the substrate scope were 20 bar of hydrogen, 75 °C and a low catalyst loading of 0.05 mol% (entry 6).

**Table 3.3**: Effect of pressure and temperature on hydrogenation of **7**.




| Entry | **6f** (mol%) | $H_2$ (bar) | temp. (°C) | t (min) | Conv. (%)[a] |
|---|---|---|---|---|---|
| 1 | 0.2 | 5 | 25 | 15 | 76 |
| 2 | 0.2 | 10 | 25 | 15 | 80 |
| 3 | 0.2 | 20 | 25 | 15 | 95 |
| 4 | 0.2 | 10 | 25 | 5 | 24 |
| 5 | 0.2 | 20 | 25 | 5 | 65 |
| 6 | 0.05 | 20 | 75 | 30 | > 99 |

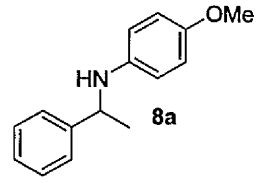
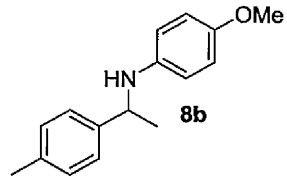
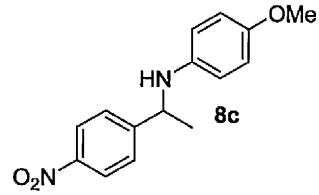
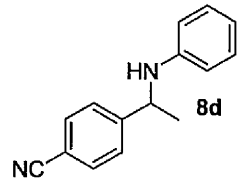
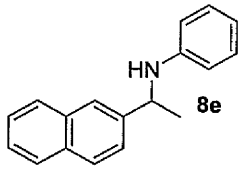
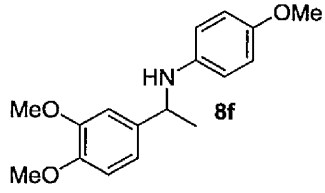
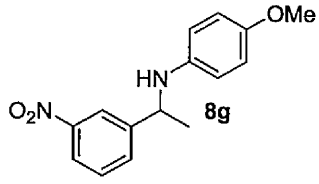
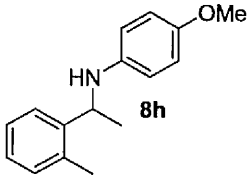
[a]Determined by $^1$H NMR.

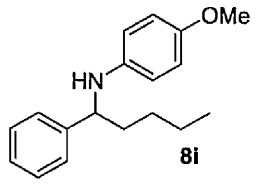
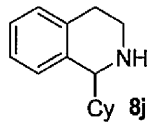
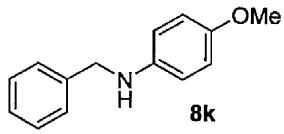
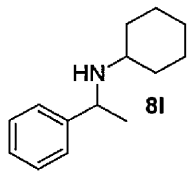
### 3.2.2 Scope of substrates

With the optimal conditions determined, a series of imine substrates were hydrogenated to demonstrate the high activity and versatility of this catalyst. At a S/C ratio of 2,000 a wide range of imines were efficiently hydrogenated, with

reaction times ranging from 5 to 75 minutes, showing the high activity and versatility of the catalyst. Table 3.4 presents the results for the hydrogenation of imines derived from aromatic ketones and an aldehyde. The catalyst tolerates functional groups with different electronic properties on the ketone (entries 1-7), although longer reaction times were required for electron-deficient ketimines (entries 1 and 2 *vs* 3 and 4). Substitution on the ketone is not restricted to the *para*-position, as the catalyst also tolerates *meta*- (entry 7), di- (entry 6) or even more sterically demanding *ortho*-substitution (entry 8). In this regard, it is worth to note that the catalyst is effective for the synthesis of sterically hindered amine **8i**. Cyclic imines can also be hydrogenated with excellent yields, albeit requiring longer reaction time (entry 10). Aldimines are particularly active under the conditions developed. Thus even at S/C of 4,000, amine **8k** was isolated in 91% yield after only 5 minutes (entry 11), resulting in a TOF of $4.4 \times 10^5$ $h^{-1}$.

**Table 3.4**: Ir-metallacycle hydrogenation of imines derived from aromatic ketones/aldehyde.[a]

| Entry | Product | t (min) | Yield (%)[b] |
|---|---|---|---|
| 1 |  **8a** | 30 | 92 |
| 2 |  **8b** | 30 | 85 |
| 3 |  **8c** | 60 | 89 |
| 4 |  **8d** | 75 | 89 |
| 5 |  **8e** | 45 | 87 |
| 6 |  **8f** | 60 | 92 |
| 7 |  **8g** | 60 | 91 |
| 8 |  **8h** | 45 | 92 |

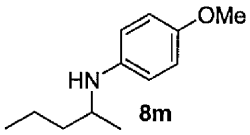
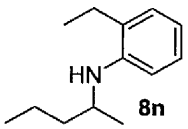
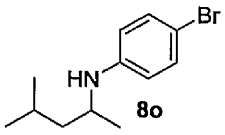
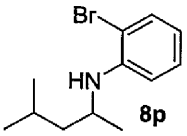
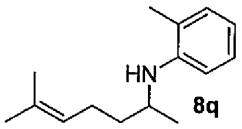
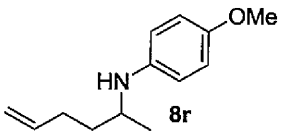
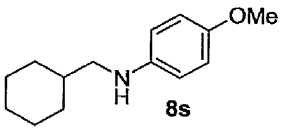
| | | | |
|---|---|---|---|
| 9 |  **8i** | 60 | 93 |
| 10 |  Cy **8j** | 120 | 95 |
| 11[c] |  **8k** | 5 | 91 |
| 12 |  **8l** | 60 | 78 |

[a]Reaction conditions: 1 mmol of imine, 0.05 mol% **6f**, 1.5 mL $CF_3CH_2OH$, 20 bar $H_2$, 75 °C, 5-75 minutes. [b]Isolated yields. [c]0.025 mol% **6f**.

Imines derived from aliphatic ketones were also hydrogenated. The results are summarised in Table 3.5. Although aliphatic ketimines tend to be more reactive than the aromatic ketimines,[8] lower yields were recorded. This is due to low stability of the aliphatic ketimines. Again, the catalyst tolerates electron-donating and electron-deficient groups in the aniline ring (entries 1 and 3,4), as well as more sterically hindered anilines (entries 2 and 4).

Worthy of note is the excellent chemoselectivity exhibited by the catalyst. Thus, C=N double bonds were reduced selectively in the presence of other reducible groups, such as internal and external alkenes (entries 5 and 6, respectively). The moderate yield obtained for imine **8r** is probably due to the instability of the corresponding imine. No reduction of the C=C double bond was observed in the crude NMR.

**Table 3.5**: Ir-metallacycle hydrogenation of imines derived from aliphatic ketones/aldehyde.[a]

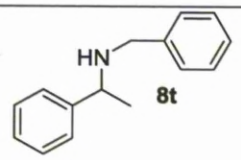
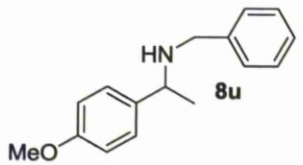
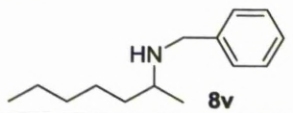
| Entry | Substrate | t (min) | Yield (%)[b] |
|---|---|---|---|
| 1 |  **8m** | 30 | 79 |
| 2 |  **8n** | 30 | 71 |
| 3 |  **8o** | 40 | 71 |
| 4 |  **8p** | 30 | 81 |
| 5 |  **8q** | 20 | 67 |
| 6 |  **8r** | 30 | 48 |
| 7[c] |  **8s** | 5 | 82 |

[a]Same conditions as those in Table 3.4. [b]Isolated yields. [c]0.025 mol% **6f**.

Finally, Table 3.6 shows the effectiveness of the catalyst for the hydrogenation of *N*-benzyl imines. The corresponding amines can then be easily debenzylated by hydrogenolysis with Pd/C. This provides a simple route for the synthesis of primary amines.[20] The catalyst is chemoselective of C=N bond as the benzyl group remains intact. Both aromatic and aliphatic ketone-

derived *N*-benzyl imines can be effectively hydrogenated under the optimised conditions with good yields.

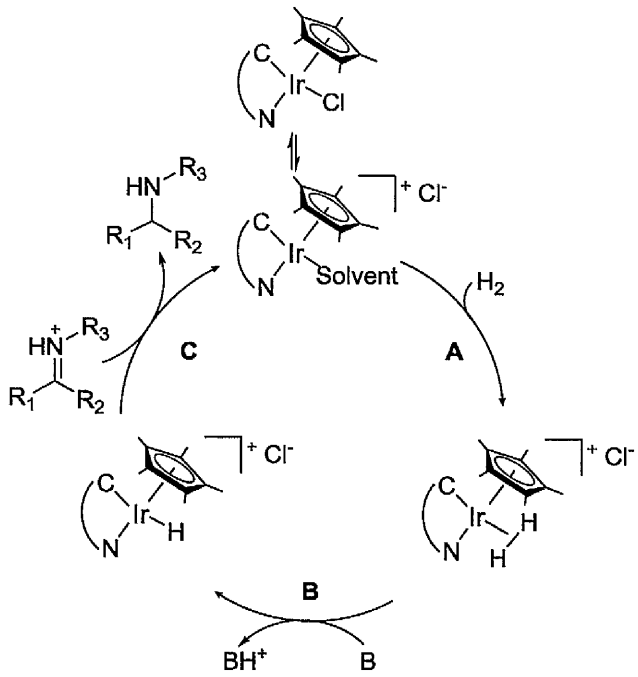
**Table 3.6**: Ir-metallacycle imine hydrogenation of *N*-benzyl imines.[a]

| Entry | Substrate | t (min) | Yield (%)[b] |
|---|---|---|---|
| 1 |  **8t** | 75 | 81 |
| 2 |  **8u** | 90 | 85 |
| 3 |  **8v** | 60 | 73 |

[a]Same conditions as those in Table 3.4. [b]Isolated yields.

### 3.2.3 Mechanisitic considerations

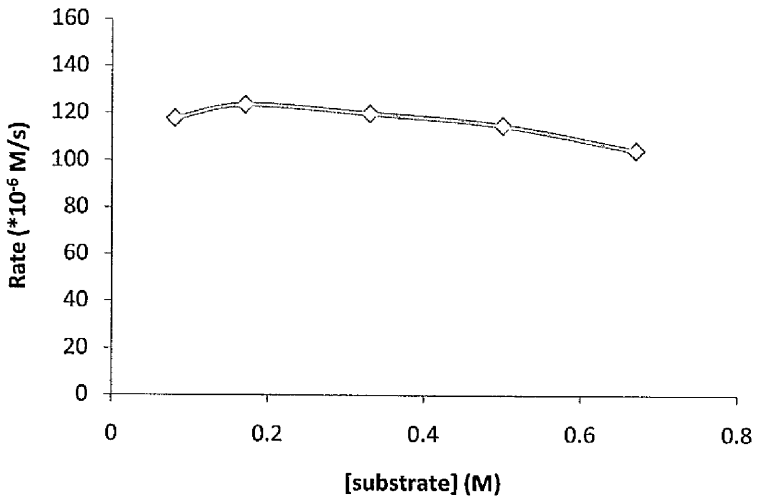
We propose that the hydrogenation with this type of catalyst takes place through an ionic pathway. As mentioned in Chapter 1, this pathway involves three main steps: hydrogen coordination (or hydrogen activation) (Step A), heterolytic cleavage of $H_2$ into $H^+$ and $H^-$ (Step B); and hydride transfer (Step C) (Scheme 3.6).




**Scheme 3.6**: Suggested catalytic cycle for Ir-metallacycle catalysed imine hydrogenation.

During the optimisation of conditions, it was shown that the increase of pressure had a positive effect on the activity, suggesting that either the $H_2$ coordination or $H_2$ cleavage would possibly be the rate-determining step. We decided to undertake some kinetic experiments to gain a deeper insight into this catalytic cycle, particularly about the rate-determining step.

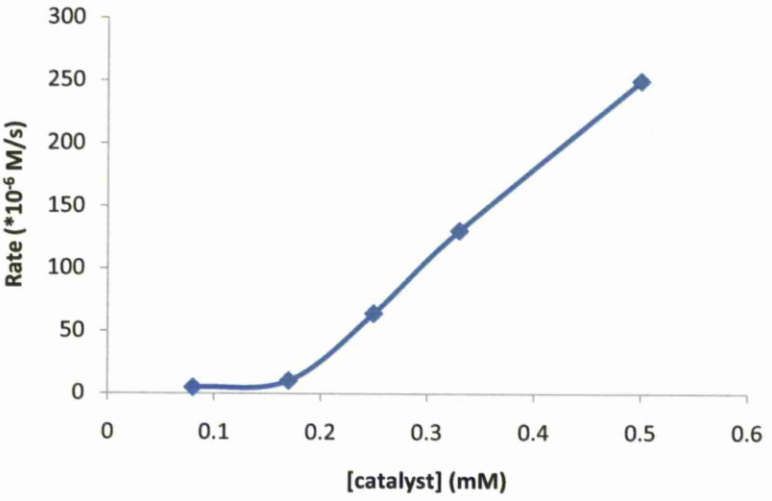
Firstly, we studied the effect of the concentration of the imine substrate on the reaction rate. For this purpose, we determined the initial rate of the reaction at different concentrations of substrates. As can be seen from the graph (Scheme 3.7), there is negligible variation on the rate when the concentration of substrate increases. This suggests that the reaction rate is zero order with respect to the imine substrate; therefore it may not participate in the rate-limiting step.




**Scheme 3.7**: Effect of the substrate concentration on the reaction rate.

In a similar way, we plotted the initial rate against different concentrations of catalyst. Scheme 3.8 shows the results obtained. The rate remains very low with limited change at very low concentrations of catalyst. We rationalise that impurities from the hydrogen gas highly affect the performance of the catalyst at very low concentrations. From 0.17 mM, there is a significant change on the initial rate when the concentration of catalyst increases. Therefore, the catalyst is involved in the rate-limiting step. This result, combined with $H_2$ pressure effect, suggests that either the coordination of $H_2$ or heterolytical cleavage of $H_2$ is the slowest step for this reduction. The heterolytical cleavage of $H_2$ requires a base to take the proton. If we assume that the substrate acts as a base and forms the corresponding iminium by protonation, then it should be first order with respect to the substrate. The fact that it is not the case suggests that rate-determining step may be hydrogen coordination. However, it has to be

taken into account that the amine product could also be involved in this step; so a final conclusion cannot be drawn.




**Scheme 3.8**: Effect of the catalyst concentration on the reaction rate.

### 3.3 Conclusions

Cyclometallated iridium complexes have shown to be highly active and chemoselective for the reduction of imines under hydrogenation conditions. The combination of air-stability, ease of synthesis and a simple work-up for the hydrogenation procedure makes this catalyst very attractive for industrial application.

Evidences from the kinetic studies suggest that the reaction rate is independent of the concentration of substrate, but dependent of both hydrogen gas and concentration of catalyst. These results support the idea of coordination of $H_2$ to the cyclometallated complex as the rate-limiting step.

## 3.4 Experimental

### General procedure for the synthesis of cyclometallated complexes[17-18]

An oven-dried Schlenk tube containing a stir bar was charged with $[IrCp^*Cl_2]_2$ (1 eq), imine ligand (2 eqs) and NaOAc (10 eqs.). Following degassing wih $N_2$ three times, freshly distilled $CH_2Cl_2$ was then injected. The resulting mixture was stirred at room temperature overnight. The reaction mixture was then filtered through celite and concentrated *in vacuo*. The resulting solid was washed with diethyl ether/hexane.

### Preparation of stock solution of cyclometallated iridium complexes

0.025 mmol of iridium complex was weighed and transferred to a 5 mL volumetric flask. 5 mL TFE was added, giving a 5 mM solution of catalyst.

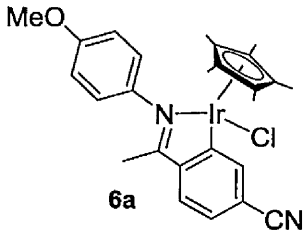
### Typical procedure for imine hydrogenation with achiral cyclometallated complexes

A glass liner containing a stir bar was charged with an imine (1 mmol) and TFE was added (0.5 mL, except for substrates **8k** and **8s** with 1 mL). The mixture was stirred until the imine was dissolved. 1 mL (0.5 mL for substrates **8k** and **8s**) of stock solution containing the catalyst was then added. The glass liner was then placed into an autoclave followed by degassing with $H_2$ three times. The hydrogenation was carried out at 20 bar $H_2$ with stirring at 75 °C for 5-75 minutes. The stirring was then stopped, and the autoclave allowed to cool down to room temperature. The hydrogen gas was then carefully released in the fumehood, the solution transferred to a flask and concentrated *in vacuo* to

afford the crude product. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (20:1 to 5:1) yielded the desired amine product.

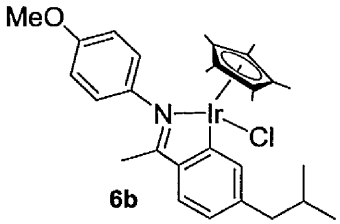
### 3.5 Analytical data

Compounds **6b**, **6e-i** and **8n-q** are new compounds.



**6a**

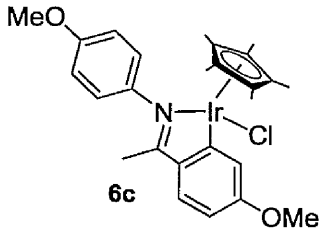
The product was obtained as a deep red solid according to the cyclometallation procedure in 17 h;[8]
**$^1$H NMR** (400 MHz, 253 K, $CDCl_3$) δ 1.44 (s, 15H), 2.47 (s, 3H), 3.88 (s, 3H), 6.82-6.83 (m, 1H), 6.93 (d, $J$ = 5.8 Hz, 1H), 7.02 (d, $J$ = 5.9 Hz, 1H), 7.33 (d, $J$ = 7.6 Hz, 1H), 7.56 (d, $J$ = 7.6 Hz, 1H), 7.77 (d, $J$ = 7.8 Hz, 1H), 8.05 (s, 1H);
**$^{13}$C NMR** (100 MHz, 253 K, $CDCl_3$) δ 8.8, 17.5, 55.7, 90.0, 112.5, 114.3, 115.1, 120.1, 123.1, 125.2, 128.2, 138.2, 138.3, 143.6, 151.8, 157.9, 167.4, 180.9;
**Anal Calcd** for $C_{26}H_{28}ClIrN_2O$: C, 51.01; H, 4.61; N, 4.58. Found: C, 51.02; H, 4.65; N, 4.42.



**6b**

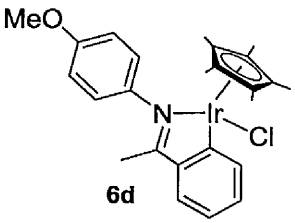
The product was obtained as a bright yellow solid according to the cyclometallation procedure in 17 h;
**$^1$H NMR** (400 MHz, 253 K, $CDCl_3$) δ 0.94 (d, $J$ = 6.7 Hz, 3H), 0.97 (d, $J$ = 6.5 Hz, 3H), 1.43 (s, 15H), 1.91-1.98 (m, 1H), 2.43 (s, 3H), 2.57-2.57 (m, 2H), 3.87 (s, 3H), 6.79 (d, $J$ = 5.4 Hz, 1H), 6.84 (d, $J$ = 7.5 Hz, 1H), 6.89 (d, $J$ = 5.4 Hz, 1H), 6.98 (d, $J$ = 6.7 Hz, 1H), 7.45 (d, $J$ = 7.5 Hz, 1H), 7.60 (s, 1H), 7.80 (d, $J$ = 6.7 Hz, 1H);
**$^{13}$C NMR** (100 MHz, 253 K, $CDCl_3$) δ 8.8, 17.1, 22.7, 23.0, 30.8, 46.1, 55.6, 88.9, 112.2, 114.8, 122.8, 123.5, 125.0, 128.3, 136.0, 144.2, 145.5, 146.0, 157.3, 167.7, 181.2;

**Anal Calcd** for $C_{29}H_{37}ClIrNO$: C, 54.15; H, 5.80; N, 2.18. Found: C, 54.66; H, 5.90; N, 2.06.



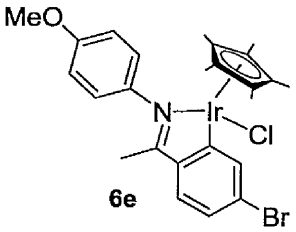
**6c**

The product was obtained as a bright yellow solid according to the cyclometallation procedure in 17 h;[8]
**$^1$H NMR** (400 MHz, 253 K, $CDCl_3$) δ 1.44 (s, 15H), 2.41 (s, 3H), 3.87 (s, 3H), 3.93 (s, 3H), 6.61 (dd, $J$ = 8.5, 2.4 Hz, 1H), 6.81 (d, $J$ = 8.4 Hz, 1H), 6.90 (d, $J$ = 8.4 Hz, 1H), 6.98 (d, $J$ = 8.4 Hz, 1H), 7.35 (d, $J$ = 2.4 Hz, 1H), 7.49 (d, $J$ = 8.5 Hz, 1H), 7.80 (d, $J$ = 8.4 Hz, 1H);
**$^{13}$C NMR** (100 MHz, 253 K, $CDCl_3$) δ 8.8, 17.1, 55.2, 55.6, 89.0, 107.6, 112.2, 114.8, 119.1, 123.8, 125.2, 130.2, 141.2, 144.2, 157.3, 161.9, 170.3, 180.1;
**Anal Calcd** for $C_{26}H_{31}ClIrNO_2$: C, 50.60; H, 5.06; N, 2.27. Found: C, 50.60; H, 4.93; N, 2.16.



**6d**

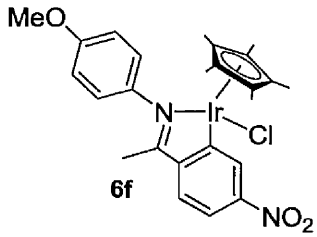
The product was obtained as a bright yellow solid according to the cyclometallation procedure in 17 h;[8]
**$^1$H NMR** (400 MHz, 253 K, $CDCl_3$) δ 1.44 (s, 15H), 2.46 (s, 3H), 3.88 (s, 3H), 6.82 (d, $J$ = 8.0 Hz, 1H), 6.91 (d, $J$ = 8.0 Hz, 1H), 6.99-7.01 (m, 1H), 7.05 (t, $J$ = 7.3 Hz, 1H), 7.26 (d, $J$ = 7.3 Hz, 1H), 7.54 (d, $J$ = 7.5 Hz, 1H), 7.80 (d, $J$ = 8.0 Hz, 1H), 7.84 (d, $J$ = 7.5 Hz, 1H);
**$^{13}$C NMR** (100 MHz, 253 K, $CDCl_3$) δ 8.8, 17.2, 55.6, 89.1, 112.3, 115.0, 121.5, 121.6, 123.5, 128.6, 132.2, 135.1, 144.1, 147.7, 157.4, 167.9, 181.6;
**Anal Calcd** for $C_{25}H_{29}ClIrNO$: C, 51.14; H, 4.98; N, 2.39. Found: C, 51.41; H, 5.04; N, 2.22.



**6e**

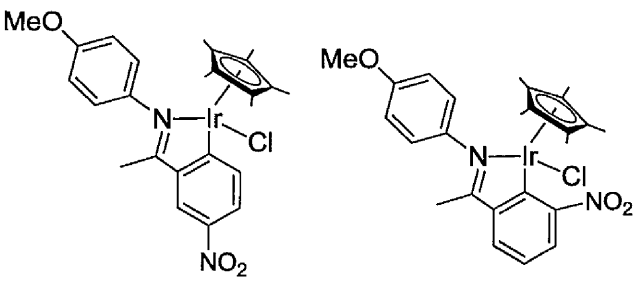
The product was obtained as a bright orange solid according to the cyclometallation procedure in 17 h;

**$^1$H NMR** (400 MHz, 253 K, $CDCl_3$) δ 1.43 (s, 15H), 2.43 (s, 3H), 3.88 (s, 3H), 6.82 (d, $J$ = 8.4 Hz, 1H), 6.91 (d, $J$ = 8.4 Hz, 1H), 7.00 (d, $J$ = 8.3 Hz, 1H), 7.18 (dd, $J$ = 8.2, 1.8 Hz, 1H), 7.39 (d, $J$ = 8.3 Hz, 1H), 7.79 (d, $J$ = 8.2 Hz, 1H), 7.91 (d, $J$ = 1.8 Hz, 1H);
**$^{13}$C NMR** (100 MHz, 253 K, $CDCl_3$) δ 8.7, 17.3, 55.6, 89.4, 112.3, 114.9, 124.5, 127.5, 130.0, 137.2, 143.8, 145.1, 146.5, 152.6, 157.6, 170.1, 180.9;
**Anal Calcd** for $C_{25}H_{28}BrIrNO$: C, 45.08; H, 4.24; N, 2.10. Found: C, 44.98; H, 4.25; N, 2.02.



**6f**

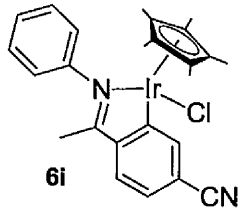
The product was obtained as a black solid according to the cyclometallation procedure in 17 h;
**$^1$H NMR** (400 MHz, 253 K, $CDCl_3$) δ 1.46 (s, 15H), 2.52 (s, 3H), 3.89 (s, 3H), 6.84-6.86 (m, 1H), 6.94-6.96 (m, 1H), 7.03 (d, $J$ = 8.6 Hz, 1H), 7.64 (d, $J$ = 8.5 Hz, 1H), 7.79 (d, $J$ = 7.8 Hz, 1H), 7.89 (dd, $J$ = 8.5, 2.2 Hz, 1H), 8.63 (d, $J$ = 2.2 Hz, 1H);
**$^{13}$C NMR** (100 MHz, 253 K, $CDCl_3$) δ 8.81, 55.7, 90.1, 112.5, 115.1, 117.1, 123.1, 124.4, 128.7, 129.2, 143.6, 148.8, 153.5, 157.9, 168.4, 180.5;
**HRMS** for $C_{25}H_{28}ClIrN_2NaO_3$ $[M+Na]^+$: Calcd: 653.1292; Found: 653.1268;
**Anal Calcd** for $C_{25}H_{15}ClIrN_2O_3$: C, 47.50; H, 4.46; N, 4.43. Found: C, 47.94; H, 4.51; N, 4.40.



**6g** **6g:6h** 7:1 **6h**

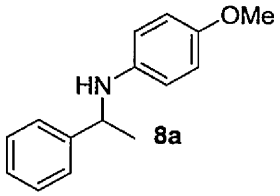
The product was obtained as a red solid according to the cyclometallation procedure in 17 h; Product exists as a mixture of regioisomers, **6g**:**6h**, 7:1;
**$^1$H NMR** (400 MHz, 253 K, $CDCl_3$) δ 1.41 (s, 1.9H), 1.44 (s, 13.1H), 2.35 (s, 0.4H), 2.55 (s, 2.6H), 3.86 (s, 0.4H), 3.88 (s, 2.6H), 6.80 (d, $J$ = 8.6 Hz, 0.3H), 6.85 (d, $J$ = 8.0 Hz, 0.8H), 6.95 (d, $J$ = 8.8 Hz, 1.2H), 7.02 (d, $J$ = 8.2 Hz, 0.8H), 7.66 (t, $J$ = 8.0 Hz, 0.2H), 7.72 (d, $J$ = 8.0 Hz, 0.8H), 7.96 (d, $J$ = 8.4 Hz, 0.8H), 8.06 (dd, $J$ = 8.4, 1.5 Hz, 0.8H), 8.35 (d, $J$ = 1.5 Hz, 1H), 8.82 (s, 0.1H);
**$^{13}$C NMR** (100 MHz, 253 K, $CDCl_3$) δ 8.8 (M), 9.0 (m), 17.4 (M), 17.7 (m), 55.6 (m), 55.7 (M), 90.2 (m), 90.6 (M), 112.5, 114.2, 115.2, 121.0, 122.2,

123.2, 123.3, 124.4, 125.1, 126.0, 129.6, 133.2, 135.7, 141.1, 142.7, 143.3, 143.5, 148.1, 148.6, 156.2, 157.9, 163.7, 173.9, 180.8, 181.1, 181.9;
**Anal Calcd** for $C_{25}H_{15}ClIrN_2O_3$: C, 47.50; H, 4.46; N, 4.43. Found: C, 47.44; H, 4.37; N, 4.41.



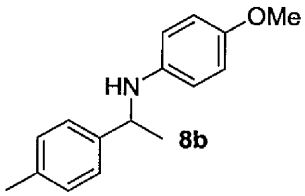
**6i**

The product was obtained as a deep red solid according to the cyclometallation procedure in 17 h;
**$^1$H NMR** (400 MHz, 253 K, $CDCl_3$) δ 1.42 (s, 15H), 2.49 (s, 3H), 6.88 (d, $J$ = 7.6 Hz, 1H), 7.27-7.31 (m, 1H), 7.35 (d, $J$ = 8.0 Hz, 1H), 7.45 (d, $J$ = 7.5 Hz, 1H), 7.52 (d, $J$ = 7.8 Hz, 1H), 7.59 (d, $J$ = 8.0 Hz, 1H), 7.80 (d, $J$ = 7.8 Hz, 1H), 8.06 (s, 1H);
**$^{13}$C NMR** (100 MHz, 253 K, $CDCl_3$) δ 3.9, 12.8, 85.2, 109.6, 115.3, 117.3, 118.3, 120.5, 122.2, 123.2, 123.6, 125.6, 133.6, 145.4, 146.9, 162.9, 176.1;
**Anal Calcd** for $C_{25}H_{26}ClIrNO_2$: C, 51.58; H, 4.50; N, 4.81. Found: C, 51.58; H, 4.44; N, 4.64.



**8a**

4-Methoxy-*N*-(1-phenylethyl)aniline.[21-22] The product (209 mg, 92% yield) was obtained as a colourless oil according to the hydrogenation procedure in 30 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.49 (d, $J$ = 6.7 Hz, 3H), 3.69 (s, 3H), 4.41 (q, $J$ = 6.7 Hz, 1H), 6.44-6.48 (m, 2H), 6.66-6.70 (m, 2H), 7.19-7.23 (m, 1H), 7.29-7.32 (m, 2H), 7.35-7.37 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 25.5, 54.7, 56.1, 115.0, 115.2, 126.3, 127.2, 129.0, 142.0, 145.9, 152.3;
**HRMS** for $C_{15}H_{18}NO$ $[M+H]^+$: Calcd: 228.1383; Found: 228.1384;
**Anal Calcd** for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.48; H, 7.74; N, 5.82.



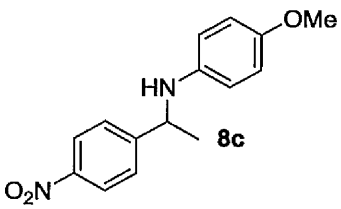

4-Methoxy-*N*-(1-p-tolylethyl)aniline.[21,23] The product (205 mg, 85% yield) was obtained as a colourless oil according to the hydrogenation procedure in 30 min;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.47 (d, $J$ = 6.7 Hz, 3H), 2.31 (s, 3H), 3.69 (s, 3H), 4.38 (q, $J$ = 6.7 Hz, 1H), 6.45-6.49 (m, 2H), 6.67-6.71 (m, 2H), 7.12 (d, $J$ = 7.9 Hz, 2H), 7.24 (d, $J$ = 7.9 Hz, 2H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.0, 25.1, 53.9, 55.7, 114.5, 114.7, 125.8, 129.3, 136.3, 141.6, 142.4, 151.8;

**HRMS** for $C_{16}H_{20}NO$ $[M+H]^+$: Calcd: 242.1540; Found: 242.1539;

**Anal Calcd** for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.03; H, 8.14; N, 5.88.



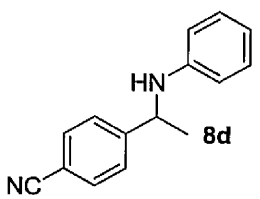

4-Methoxy-*N*-(1-(4-nitrophenyl)ethyl)aniline.[21,23] The product (242 mg, 89% yield) was obtained as a yellow oil according to the hydrogenation procedure in 60 min;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.52 (d, $J$ = 6.8 Hz, 3H), 3.69 (s, 3H), 3.84 (brs, 1H), 4.49 (q, $J$ = 6.8 Hz, 1H), 6.38-6.42 (m, 2H), 6.67-6.71 (m, 2H), 7.52-7.56 (m, 2H), 8.16-8.19 (m, 2H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 25.4, 54.4, 56.1, 114.9, 115.2, 124.5, 127.1, 141.1, 147.4, 152.7, 153.9;

**HRMS** for $C_{15}H_{17}N_2O_3$ $[M+H]^+$: Calcd: 273.1239; Found: 273.1241;

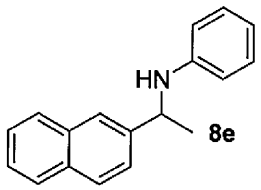
**Anal Calcd** for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.80; H, 5.95; N, 10.12.



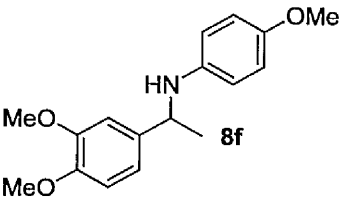

4-(1-(Phenylamino)ethyl)benzonitrile.[24] The product (197 mg, 89% yield) was obtained as a colourless oil according to the hydrogenation procedure in 75 min;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.52 (d, $J$ = 6.8 Hz, 3H), 4.04 (brs, 1H), 4.51 (q, $J$ = 6.8 Hz, 1H), 6.43 (dd, $J$ = 8.6, 0.9 Hz, 2H), 6.68 (tt, $J$ = 7.3, 0.9 Hz, 1H), 7.07-7.12 (m, 2H), 7.47-7.50 (m, 2H), 7.60-7.62 (m, 2H);

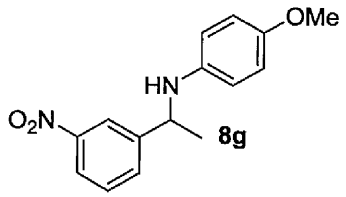
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 25.3, 53.8, 111.2, 113.7, 118.3, 119.3, 127.0, 129.6, 133.0, 147.0, 151.4;
**HRMS** for $C_{15}H_{15}N_2$ $[M+H]^+$: Calcd: 223.1230; Found: 223.1232;
**Anal Calcd** for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.50. Found: C, 81.02; H, 6.34; N, 12.73.




*N*-(1-(Naphthalen-2-yl)ethyl)aniline.[21,25] The product (215 mg, 87% yield) was obtained as a colourless oil according to the hydrogenation procedure in 45 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.57 (d, $J$ = 6.7 Hz, 3H), 4.10 (brs, 1H), 4.62 (q, $J$ = 6.7 Hz, 1H), 6.54 (dd, $J$ = 8.6, 1.0 Hz, 2H), 6.63 (tt, $J$ = 7.3, 1.0 Hz, 1H), 7.04-7.09 (m, 2H), 7.39-7.46 (m, 2H), 7.48 (dd, $J$ = 8.5, 1.6 Hz, 1H), 7.77-7.81 (m, 4H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 25.5, 54.2, 113.8, 117.8, 124.7, 124.9, 125.9, 126.4, 128.1, 128.3, 128.9, 129.6, 133.2, 134.0, 143.2, 147.8;
**HRMS** for $C_{18}H_{18}N$ $[M+H]^+$: Calcd: 248.1434; Found: 248.1436;
**Anal Calcd** for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66. Found: C, 87.31; H, 6.96; N, 5.55.




*N*-(1-(3,4-Dimethoxyphenyl)ethyl)-4-methoxyaniline.[21,23] The product (264 mg, 92% yield) was obtained as a colourless oil according to the hydrogenation procedure in 60 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.49 (d, $J$ = 6.6 Hz, 3H), 3.70 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.35 (q, $J$ = 6.6 Hz, 1H), 6.47-6.51 (m, 2H), 6.68-6.72 (m, 2H), 6.81 (d, $J$ = 6.7 Hz, 1H), 6.88-6.92 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 25.5, 54.6, 56.1, 56.2(6), 56.2(9), 109.6, 111.7, 115.1, 115.2, 118.2, 138.5, 142.0, 148.2, 149.6, 152.4;
**HRMS** for $C_{17}H_{21}NO_3Na$ $[M+Na]^+$: Calcd: 310.1419; Found: 310.1430;
**Anal Calcd** for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.10; H, 7.10; N, 4.35.




**8g**

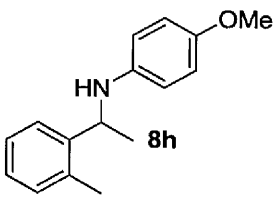
4-Methoxy-*N*-(1-(3-nitrophenyl)ethyl)aniline.[21,23] The product (247 mg, 91% yield) was obtained as a yellow oil according to the hydrogenation procedure in 60 min;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.51 (d, $J$ = 6.7 Hz, 3H), 3.67 (s, 3H), 4.49 (q, $J$ = 6.7 Hz, 1H), 6.41-6.45 (m, 2H), 6.67-6.71 (m, 2H), 7.45 (t, $J$ = 7.9 Hz, 1H), 7.70 (d, $J$ = 7.7 Hz, 1H), 8.06 (ddd, $J$ = 8.1, 2.3, 1.0 Hz, 1H), 8.24 (t, $J$ = 2.3 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 25.5, 54.3, 56.1, 115.0, 115.2, 121.4, 122.5, 130.1, 132.7, 141.2, 148.6, 149.1, 152.7;

**HRMS** for $C_{15}H_{17}N_2O_3$ $[M+H]^+$: Calcd: 273.1239; Found: 273.1235;

**Anal Calcd** for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.62; H, 6.17; N, 10.21.




**8h**

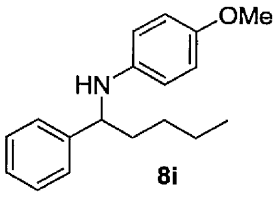
4-Methoxy-*N*-(1-o-tolylethyl)aniline.[21,26] The product (222 mg, 92% yield) was obtained as a colourless oil according to the hydrogenation procedure in 45 min;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.41 (dd, $J$ = 6.6, 1.1 Hz, 3H), 2.40 (d, $J$ = 0.9 Hz, 3H), 3.63 (d, $J$ = 0.9 Hz, 3H), 3.72 (brs, 1H), 4.57 (q, $J$ = 6.5 Hz, 1H), 6.35-6.40 (m, 2H), 6.64-6.67 (m, 2H), 7.07-7.14 (m, 3H), 7.40 (d, $J$ = 7.3 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 19.5, 23.6, 51.0, 56.2, 114.8, 115.3, 125.2, 127.0(8), 127.1(2), 131.1, 135.1, 142.0, 143.5, 152.4;

**HRMS** for $C_{16}H_{20}NO$ $[M+H]^+$: Calcd: 242.1539; Found: 242.1535;

**Anal Calcd** for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 78.52; H, 8.25; N, 5.89.

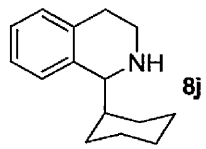



**8i**

4-Methoxy-*N*-(1-phenylpentyl)aniline.[27] The product (251 mg, 93% yield) was obtained according to the hydrogenation procedure yellow oil in 60 min;

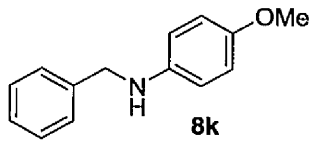
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.87 (t, $J$ = 7.0 Hz, 3H), 1.21-1.41 (m, 4H), 1.68-1.82 (m, 2H), 3.65 (s, 3H), 4.20 (t, $J$ = 6.8 Hz, 1H), 6.43-6.47 (m, 2H), 6.64-6.68 (m, 2H), 7.16-7.21 (m, 1H), 7.26-7.33 (m, 4H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 14.5, 23.1, 29.0, 39.2, 56.2, 59.5, 114.9, 115.2, 126.9, 127.3, 129.0, 142.3, 145.1, 152.3;
**HRMS** for $C_{18}H_{24}NO$ $[M+H]^+$: Calcd: 270.1852; Found: 270.1847;
**Anal Calcd** for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.02; H, 8.86; N, 5.48.



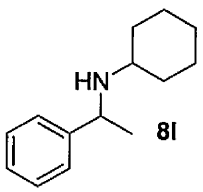

**8j**

1-Cyclohexyl-1,2,3,4-tetrahydroisoquinoline.[28] The product (251 mg, 93% yield) was obtained as a colourless oil according to the hydrogenation procedure in 60 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.06-1.19 (m, 3H), 1.28-1.42 (m, 3H), 1.65-1.73 (m, 3H), 1.80-1.84 (m, 1H), 1.88-1.92 (m, 1H), 2.15 (brs, 1H), 2.65 (dt, $J$ = 15.6, 4.4 Hz, 1H), 2.78-2.86 (m, 1H), 2.88-2.95 (m, 1H), 3.23-3.30 (m, 1H), 3.91 (d, $J$ = 4.4 Hz, 1H), 7.04-7.14 (m, 4H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 26.8, 27.0, 27.1, 27.5, 30.7, 31.4, 42.8, 43.4, 61.2, 125.9, 126.0, 126.5, 129.6, 136.7, 138.9;
**HRMS** for $C_{15}H_{22}N$ $[M+H]^+$: Calcd: 216.1747; Found: 216.1747;
**Anal Calcd** for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50. Found: C, 80.83; H, 9.50; N, 6.23.




**8k**

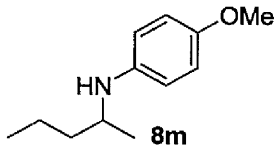
*N*-Benzyl-4-methoxyaniline.[8,29] The product (194 mg, 91% yield) was obtained according to the hydrogenation procedure as a colourless oil in 5 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 4.27 (s, 2H), 6.58-6.61 (m, 2H), 6.75-6.79 (m, 2H), 7.23-7.28 (m, 1H), 7.31-7.38 (m, 4H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 49.7, 56.2, 114.5, 115.3, 127.6, 128.0, 129.0, 140.1, 142.9, 152.6;
**HRMS** for $C_{14}H_{16}NO$ $[M+H]^+$: Calcd: 214.1226; Found: 214.1227;
**Anal Calcd** for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.57; H, 7.26; N, 6.77.




**8l**

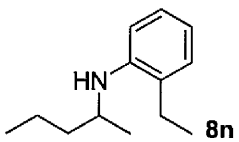
*N*-(1-Phenylethyl)cyclohexanamine.[8] The product (159 mg, 78% yield) was obtained according to the general procedure as a colourless oil in 60 min;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.98-1.17 (m, 5H), 1.32 (d, $J$ = 6.6 Hz, 3H), 1.54-1.55 (m, 1H), 1.63-1.71 (m, 3H), 1.96-2.00 (m, 1H), 2.23-2.30 (m, 1H), 3.95 (q, $J$ = 6.6 Hz, 1H), 7.20-7.25 (m, 1H), 7.27-7.33 (m, 4H);
**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 25.4, 25.5, 25.7, 26.6, 33.6, 35.0, 54.0, 54.8, 126.9, 127.1, 128.8, 146.7;
**HRMS** for $C_{14}H_{22}N$ $[M+H]^+$: Calcd: 214.1752; Found: 214.1755;
**Anal Calcd** for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.86; H, 10.42; N, 6.96.



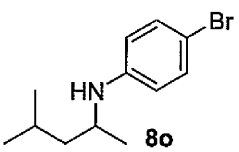
**8m**

4-Methoxy-*N*-(pentan-2-yl)aniline.[30] The product (152 mg, 79% yield) was obtained according to the general procedure as a colourless oil in 30 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.92 (t, $J$ = 7.1 Hz, 3H), 1.14 (d, $J$ = 6.2 Hz, 3H), 1.34-1.44 (m, 3H), 1.50-1.57 (m, 1H), 3.37 (sextet, $J$ = 6.2 Hz, 1H), 3.74 (s, 3H), 6.53-6.58 (m, 2H), 6.75-6.79 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 14.1, 19.3, 20.8, 39.4, 49.3, 55.8, 114.7, 114.9, 141.9, 151.8;
**HRMS** for $C_{12}H_{20}NO$ $[M+H]^+$: Calcd: 194.1539; Found: 194.1534;
**Anal Calcd** for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 73.95; H, 10.20; N, 7.20.



**8n**

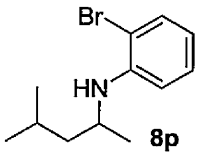
2-Ethyl-*N*-(pentan-2-yl)aniline. The product (136 mg, 71% yield) was obtained according to the general procedure as a colourless oil in 30 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.93 (t, $J$ = 7.2 Hz, 3H), 1.19 (d, $J$ = 6.3 Hz, 3H), 1.24 (t, $J$ = 7.5 Hz, 3H), 1.36-1.49 (m, 3H), 1.54-1.63 (m, 1H), 2.45 (q, $J$ = 7.5 Hz, 2H), 3.38 (brs, 1H), 3.49-3.57 (m, 1H), 6.62 (d, $J$ = 8.4 Hz, 1H), 6.66 (td, $J$ = 7.4, 1.0 Hz, 1H), 7.06 (dd, $J$ = 7.4, 1.5 Hz, 1H), 7.10 (td, $J$ = 7.7, 1.5 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 12.8, 14.2, 19.4, 20.9, 23.9, 39.6, 47.9, 110.3, 116.3, 126.9, 127.2, 128.0, 144.9;
**HRMS** for $C_{13}H_{22}N$ $[M+H]^+$: Calcd: 192.1747; Found: 192.1747;
**Anal Calcd** for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.32. Found: C, 81.63; H, 11.48; N, 7.61.



**8o**

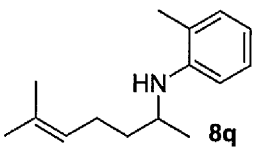
1-Bromo-4-(2,4-dimethylpentyl)benzene. The product (182 mg, 71% yield) was obtained according to the general procedure as a colourless oil in 40 min;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.90 (d, $J$ = 6.6 Hz, 3H), 0.93 (d, $J$ = 6.6 Hz, 3H), 1.13 (d, $J$ = 6.2 Hz, 3H), 1.25 (dt, $J$ = 13.7, 6.9 Hz, 1H), 1.44 (dt, $J$ = 13.7, 6.9 Hz, 1H), 1.67-1.78 (m, 1H), 3.39 (brs, 1H), 3.42-3.50 (m, 1H), 6.42-6.46 (m, 2H), 7.20-7.25 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.3, 23.0, 23.3, 25.5, 47.0, 47.1, 108.5, 114.9, 132.3, 147.1;
**HRMS** for $C_{12}H_{19}BrN$ $[M+H]^+$: Calcd: 256.0695; Found: 256.0696;
**Anal Calcd** for $C_{12}H_{19}BrN$: C, 56.26; H, 7.03; N, 5.47. Found: C, 56.63; H, 7.23; N, 5.82.



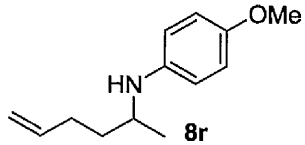
**8p**

2-Bromo-*N*-(4-methylpentan-2-yl)aniline. The product (207 mg, 81% yield) was obtained according to the general procedure as a colourless oil in 30 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.91 (d, $J$ = 6.6 Hz, 3H), 0.96 (d, $J$ = 6.6 Hz, 3H), 1.19 (d, $J$ = 6.2 Hz, 3H), 1.33 (dt, $J$ = 13.9, 6.9 Hz, 1H), 1.52 (dt, $J$ = 13.9, 7.0 Hz, 1H), 1.72-1.82 (m, 1H), 3.50-3.60 (m, 1H), 4.09 (brd, $J$ = 7.3 Hz, 1H), 6.51 (ddd, $J$ = 7.8, 7.3, 1.3 Hz, 1H), 6.63 (dd, $J$ = 7.9, 1.3 Hz, 1H), 7.15 (ddd, $J$ = 7.9, 7.3, 1.5 Hz, 1H), 7.40 (dd, $J$ = 7.8, 1.5 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.4, 23.0, 23.3, 25.5, 47.1, 110.2, 111.9, 117.4, 128.8, 132.9, 144.8;
**HRMS** for $C_{12}H_{19}BrN$ $[M+H]^+$: Calcd: 256.0695; Found: 256.0690;
**Anal Calcd** for $C_{12}H_{19}BrN$: C, 56.26; H, 7.03; N, 5.47. Found: C, 56.37; H, 7.41; N, 5.79.



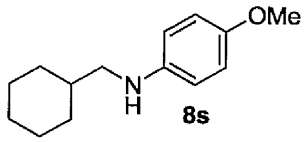
**8q**

2-Methyl-*N*-(6-methylhept-5-en-2-yl)aniline. The product (145 mg, 67% yield) was obtained according to the general procedure as a colourless oil in 20 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.20 (d, $J$ = 6.3 Hz, 3H), 1.46-1.55 (m, 1H), 1.58 (s, 3H), 1.59-1.66 (m, 1H), 1.69 (d, $J$ = 0.8 Hz, 3H), 2.06-2.13 (m, 2H), 2.11 (s, 3H), 3.30 (brs, 1H), 3.52 (sextet, $J$ = 6.3 Hz, 1H), 5.12-5.16 (m, 1H), 6.58-6.62 (m, 2H), 7.03 (d, $J$ = 7.1 Hz, 1H), 7.10 (td, $J$ = 7.8, 1.2 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 17.6(0), 17.6(5), 20.9, 24.7, 25.7, 37.3, 47.8, 110.0, 116.1, 121.6, 124.0, 127.1, 130.2, 132.0, 145.5;
**HRMS** for $C_{15}H_{24}N$ $[M+H]^+$: Calcd: 218.1901; Found: 218.1903;
**Anal Calcd** for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.44. Found: C, 82.56; H, 10.92; N, 6.82.



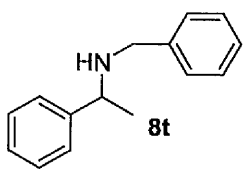

**8r**

*N*-(Hex-5-en-2-yl)-4-methoxyaniline.[22,30] The product (98 mg, 48% yield) was obtained according to the general procedure as a colourless oil in 30 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.08 (d, $J$ = 6.3 Hz, 3H), 1.38-1.47 (m, 1H), 1.53-1.62 (m, 1H), 2.05-2.11 (m, 2H), 3.40 (sextet, $J$ = 6.3 Hz, 1H), 3.74 (s, 3H), 4.89 (d, $J$ = 10.1 Hz, 1H), 4.95 (dd, $J$ = 17.0, 1.6 Hz, 1H), 5.75 (ddt, $J$ = 17.0, 10.3, 6.7 Hz, 1H), 6.45-6.49 (m, 2H), 6.67-6.71 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.1, 30.8, 36.6, 49.6, 56.2, 115.2, 115.3(2), 115.3(5), 138.8, 142.0, 152.4;
**HRMS** for $C_{13}H_{20}NO$ $[M+H]^+$: Calcd: 206.1539; Found: 206.1540;
**Anal Calcd** for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.18; H, 9.50; N, 7.00.



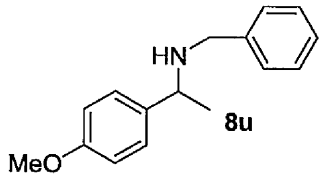

**8s**

*N*-(Cyclohexylmethyl)-4-methoxyaniline.[31] The product (180 mg, 82% yield) was obtained according to the general procedure as a colourless oil in 5 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.89-1.06 (m, 2H), 1.15-1.34 (m, 3H), 1.54-1.64 (m, 1H), 1.68-1.85 (m, 5H), 2.93 (d, $J$ = 6.6 Hz, 2H), 3.46 (brs, 1H), 3.72 (s, 3H), 6.59 (d, $J$ = 8.8 Hz, 2H), 6.78-6.82 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 26.0, 26.6, 31.3, 37.6, 51.7, 55.9, 113.9, 114.9, 143.0, 151.8;
**HRMS** for $C_{14}H_{22}NO$ $[M+H]^+$: Calcd: 220.1696; Found: 220.1692;
**Anal Calcd** for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.60; H, 9.81; N, 6.07.



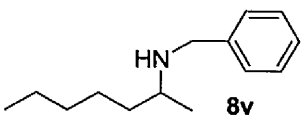

**8t**

*N*-Benzyl-1-phenylethanamine.[8] The product (171 mg, 81% yield) was obtained according to the general procedure as a colourless oil in 75 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.29 (d, $J$ = 6.6 Hz, 3H), 3.51 (d, A of AB, $J_{AB}$ = 13.1 Hz, 1H), 3.58 (d, B of AB, $J_{AB}$ = 13.1 Hz, 1H), 3.73 (q, $J$ = 6.6 Hz, 1H), 7.13-7.27 (m, 10H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 23.4, 50.6, 56.4, 125.7, 125.8, 125.9, 127.1, 127.3, 127.4, 139.5, 144.4;
**HRMS** for $C_{15}H_{18}N$ $[M+H]^+$: Calcd: 212.1434; Found: 212.1429;
**Anal Calcd** for $C_{15}H_{17}NO$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.56; H, 8.19; N, 6.50.




**8u**

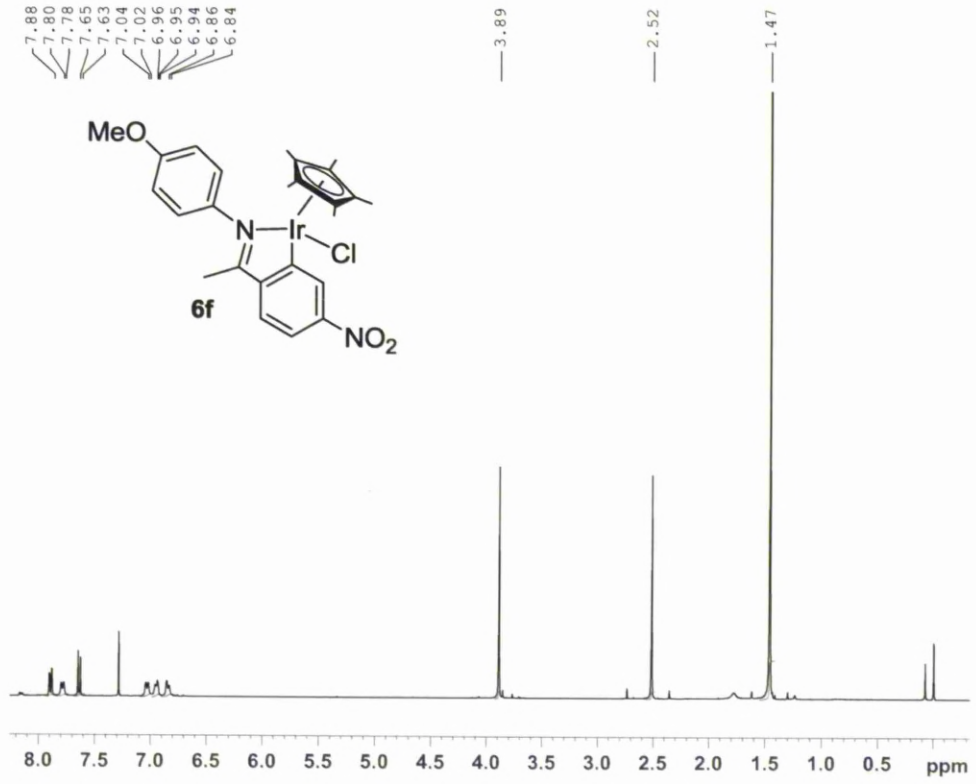
*N*-Benzyl-1-(4-methoxyphenyl)ethanamine.[32] The product (205 mg, 85% yield) was obtained according to the general procedure as a colourless oil in 90 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.34 (d, $J$ = 6.5 Hz, 3H), 3.58 (d, A of AB, $J_{AB}$ = 13.1 Hz, 1H), 3.65 (d, B of AB, $J_{AB}$ = 13.1 Hz, 1H), 3.77 (q, $J$ = 6.5 Hz, 1H), 3.81 (s, 3H), 6.87-6.91 (m, 2H), 7.21-7.34 (m, 7H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 24.9, 52.0, 55.7, 57.2, 114.2, 127.2, 128.1, 128.5, 128.8, 138.1, 141.2, 159.2;
**HRMS** for $C_{16}H_{20}NO$ $[M+H]^+$: Calcd: 242.1539; Found: 242.1543;
**Anal Calcd** for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.13; H, 8.37; N, 5.84.

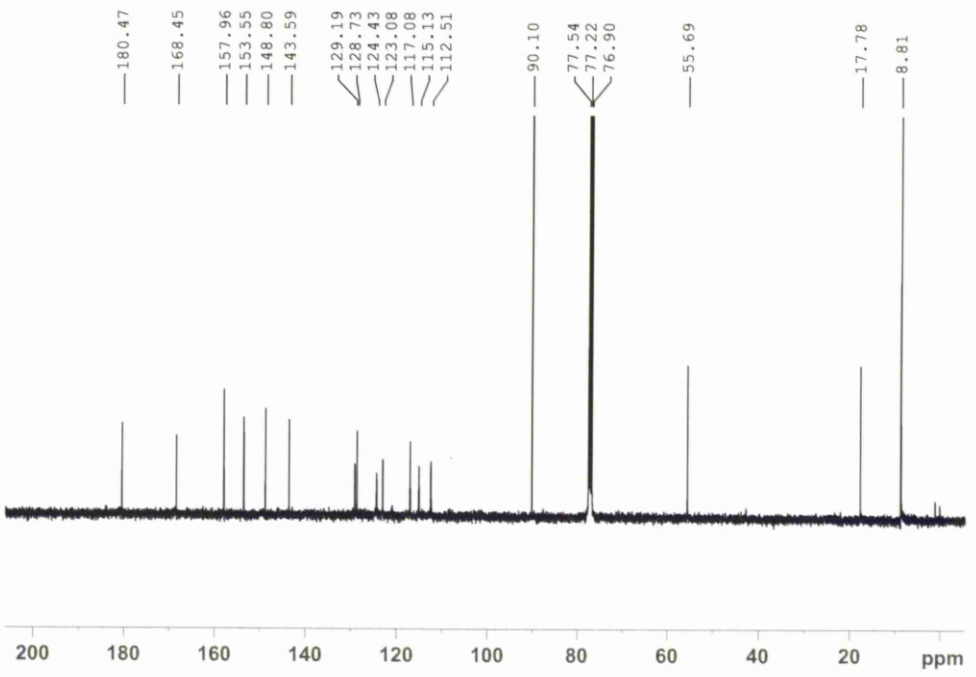



**8v**

*N*-Benzylheptan-2-amine.[8,33] The product (150 mg, 73% yield) was obtained according to the general procedure as a yellow oil in 60 min;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, $J$ = 6.9 Hz, 3H), 1.08 (d, $J$ = 6.2 Hz, 3H), 1.22-1.34 (m, 8H, including NH), 1.42-1.52 (m, 1H), 2.60-2.71 (m, 1H), 3.74 (d, A of AB, $J_{AB}$ = 12.9 Hz, 1H), 3.83 (d, B of AB, $J_{AB}$ = 12.9 Hz, 1H), 7.22-7.27 (m, 1H), 7.31-7.35 (m, 4H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 14.5, 20.7, 23.1, 26.1, 32.5, 37.4, 51.8, 52.9, 127.2, 128.6, 128.8, 141.2;
**HRMS** for $C_{14}H_{24}N$ $[M+H]^+$: Calcd: 206.1903; Found: 206.1903;
**Anal Calcd** for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.62; H, 11.02; N, 6.37.

## 3.6 $^{1}H$ and $^{13}C$ NMR spectra of complex 6f



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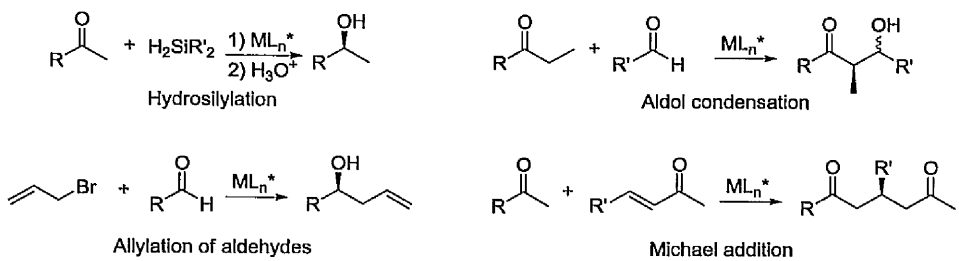
# Chapter 4

# Chiral Cyclometallated Ir-Oxazoline Complexes for Asymmetric Imine Hydrogenation

## 4.1 Introduction

Chapter 3 showed excellent results for the hydrogenation of imines with achiral cyclometallated iridium complexes, where both *N*-aryl and *N*-alkylimines can be hydrogenated in TFE. This prompted us to develop chiral cyclometallated iridium complexes for the asymmetric hydrogenation of *N*-alkyl imines. This type of substrates proved to be one of the main limitations for the cooperative chiral Ir-phosphate catalysis described in Chapter 2, as the catalyst is ineffective for DARA with aliphatic amines. This chapter describes the efforts towards highly enantioselective hydrogenation of *N*-alkyl imines with chiral Ir-oxazoline catalysts synthesised by cyclometallation of an iridium metal centre with oxazoline ligands.

Chiral oxazoline-containing ligands have proven highly versatile in asymmetric catalysis. They are present in a wide variety of catalytic applications, as for example hydrosilylation,[1-2] aldol condensation,[3-6] allylation of aldehydes,[7] allylic substitution[8-13] and Michael additions (Scheme 4.1).[14-15]




**Scheme 4.1**: Example of catalytic applications of chiral oxazoline ligands.

Pyridinooxazoline[16-17] (PyOX) **1**, bisoxazoline[18] **2**, *N,N,N*-bis(oxazolinylphenyl)amine[19-21] (BOPA) **3**, bisoxazolinopyridine[22] (PyBOX) **4** and PHOX ligands are some of the most widely used oxazoline-containing ligands (Figure 4.1). PHOX ligands, in particular, have been proven very efficient ligands for the asymmetric hydrogenation of imines,[23-30] as presented in the introduction of this thesis. Additionally, the wide use of chiral-oxazoline ligands for asymmetric transformations was mentioned above. Therefore, the introduction to this chapter will only present relevant examples of chiral metal-oxazoline catalysts used for catalytic asymmetric reduction.

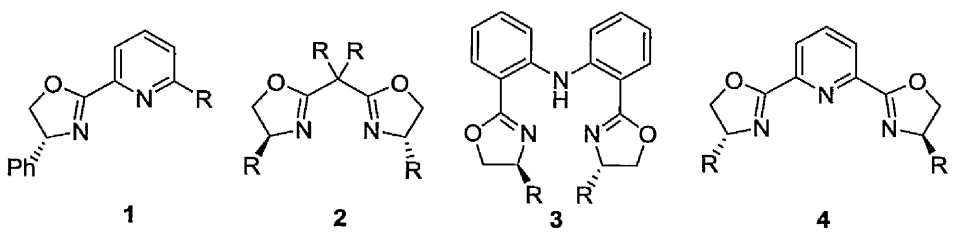
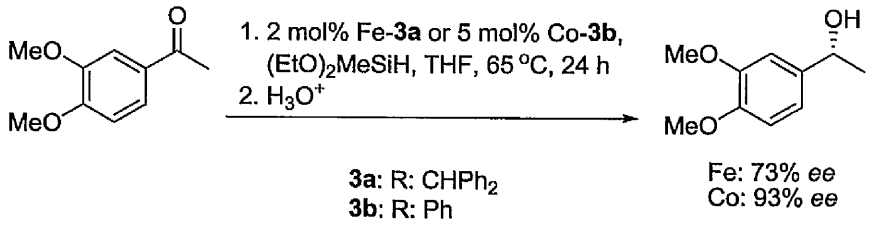



**Figure 4.1**: Examples of oxazoline-containing ligands.

Brunner studied the asymmetric hydrosilylation of acetophenone with a rhodium catalyst containing a derivative of ligand **1**.[16] This is one of the first examples of an oxazoline-containing ligand applied to asymmetric hydrosilylation. The best enantioselectivity was obtained when **1** had R = Me, although only 48% *ee* was reported.

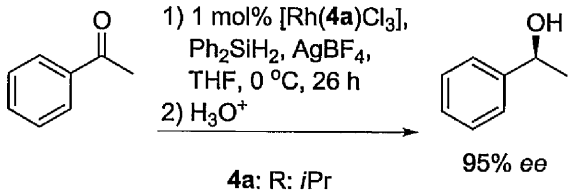
Nishiyama and co-workers reported iron[31-32] and cobalt[31] catalysts containing a BOPA ligand **3** for the hydrosilylation of ketones. Alcohol products are obtained with good yields and enantioselectivities, with 2-5 mol%

catalyst loading, at 65 °C, albeit with long reaction times (24-96 hours) (Scheme 4.2).



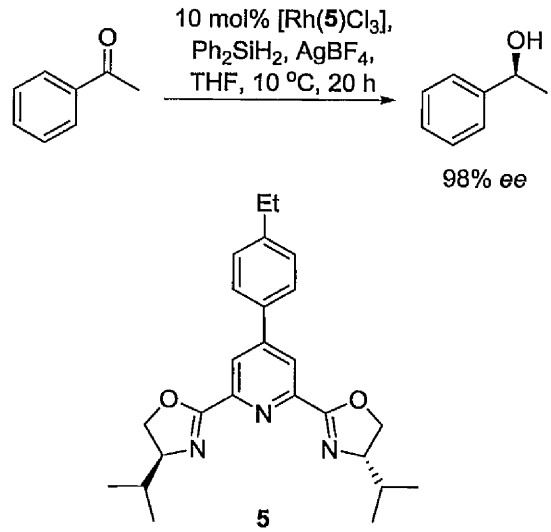

**Scheme 4.2**: Asymmetric hydrosilylation of ketones with Fe or Co-BOPA catalysts.

PyBOX ligands were first prepared by Nishiyama in 1989.[33] Since then, the use of these ligands has increased exponentially. They are effective chiral ligands in a wide variety of transformations.[22] In the area of asymmetric reduction, Nishiyama and co-workers reported the first asymmetric hydrosilylation of ketones with rhodium-PyBOX catalysts[33] and further developed this work in the following years.[2,34] By using 1 mol% of a Rh-PyBOX **4a** catalyst with the aid of $AgBF_4$, a wide range of aromatic and aliphatic methyl ketones were reduced with high enantioselectivities (68-99% *ee*) (Scheme 4.3).[2] The presence of the silver salt is essential to activate the catalyst, enabling the formation of the corresponding cationic rhodium species, which then can react smoothly with the silane.




**Scheme 4.3**: Asymmetric hydrosilylation of ketones with a Rh-PyBOX catalyst.

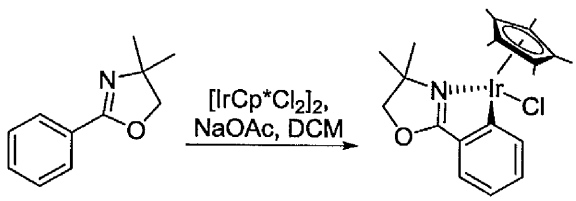
More recently, Jayashankaran and co-workers reported the synthesis of PyBOX-derived ligands **5** and studied their application in the rhodium-catalysed hydrosilylation of ketones (Scheme 4.4).[35] These new ligands contain a remote substituent, at the *para*-position of the pyridine. Although far away from the catalytic centre, it is connected through an extended π-conjugation, so it influences the electronic environment at the metal centre. The reaction is completed after 20 hours in THF at 10 °C. Enantioselectivities surpassed in general those obtained by Nishiyama's group (87-99% *ee*) but a higher catalyst loading was required (10 mol%).




**Scheme 4.4**: Hydrosilylation of ketones with a derivative of PyBOX ligand.

To the best of our knowledge, there are no examples of the study of the catalytic activity of oxazoline-containing ligands where the ligand is cyclometallated. The cyclometallation of an oxazoline to $[IrCp^*Cl_2]_2$ was firstly reported by Davies *et al.* (Scheme 4.5).[36-37] More recently, they studied

the formation of the corresponding cationic species of **6**, which was followed by insertion reaction with internal and terminal alkynes.[38] All complexes were fully characterised but never tested for catalytic activity. This chapter presents the effort made in the design and synthesis of chiral cyclometallated Ir-oxazoline complexes and the study of asymmetric hydrogenation of an *N*-benzyl imine with these complexes.

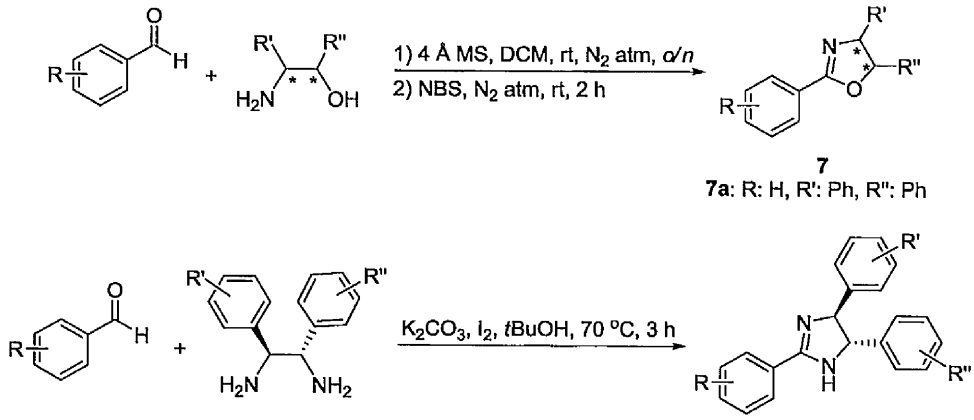



**6**

**Scheme 4.5**: Cyclometallated Ir-oxazoline complex synthesised by Davies.

## 4.2 Results and Discussion

A series of chiral oxazolines were synthesised from aromatic aldehydes and chiral aminoalcohols, following a procedure developed by Glorius *et al.* (Scheme 4.6).[39] In addition, chiral imidazolidine ligands were also synthesised by other members of the group from aromatic aldehydes and chiral diamines, following a known procedure.[40] They were used to form cyclometallated iridium complexes and tested for asymmetric hydrogenation of imines.




**Scheme 4.6**: Synthesis of chiral oxazoline and imidazolidine ligands.

The oxazoline ligands synthesised were cyclometallated with $[IrCp^*Cl_2]_2$ in the presence of NaOAc, following the same procedure presented in Chapter 3.[36] The cyclometallation took place exclusively at the aromatic ring derived from the aldehyde.[41] It was observed that two different diastereoisomers were formed. The diastereomeric ratio varies from 1:1 to 4:1 depending on the substituents; it is 2:1 for **8a**:**8b** (Figure 4.2). When cyclometallation was carried out, the solid obtained as a product was washed with hexane/ether and used for the hydrogenation reactions.

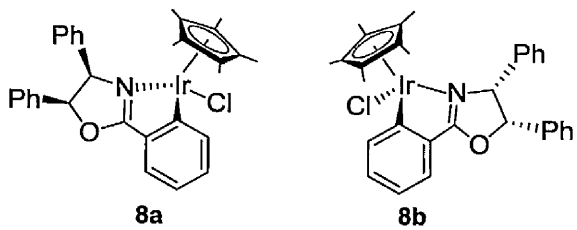
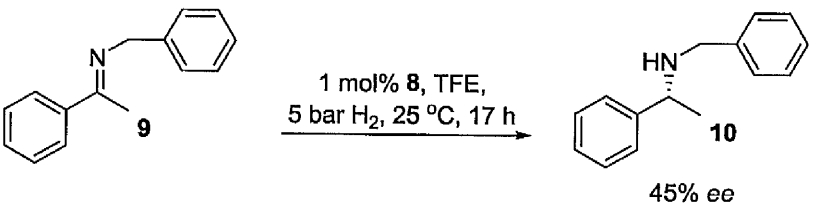



**Figure 4.2**: Diastereoisomers observed in chiral cyclometallated Ir-oxazoline complexes.

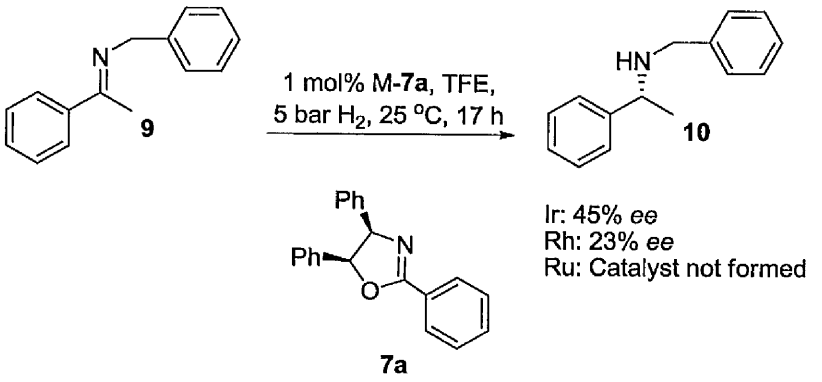
In a preliminary study, we applied the mixture of diastereoisomers **8** to asymmetric hydrogenation of imine **9** (Scheme 4.7). A promising 45% *ee* was

obtained at 5 bar $H_2$ and 25 °C with 1 mol% catalyst loading. This encouraged us to modify the oxazoline ligand backbone in order to increase the enantioselectivity. One of the main features of the oxazoline ligands is their modular structure. Their structure can be easily modified with different substituents in the aldehyde and/or amino alcohol moiety. In addition, different metal precursors can be applied.



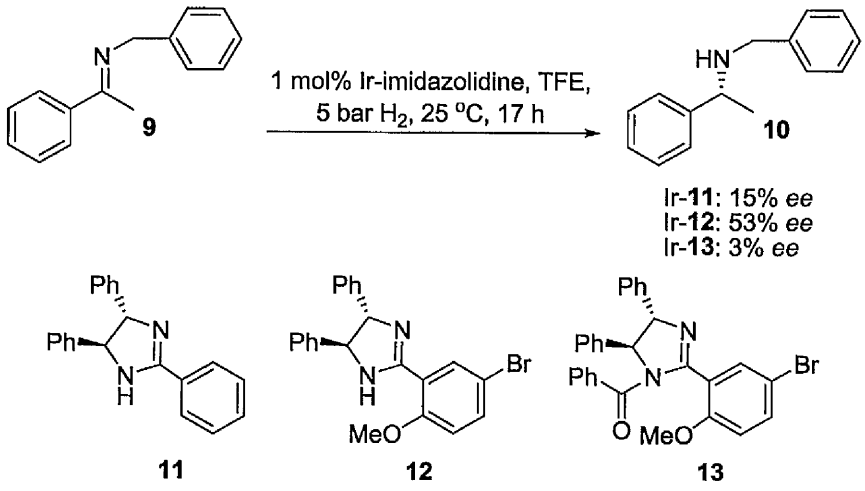

**Scheme 4.7:** Initial study on asymmetric hydrogenation of imine with an Ir-oxazoline complex.

Firstly, the effect of the metal centre on the enantioselectivity was studied. Specifically cyclometallated Rh, Ir and Ru metal centres were compared. Cyclometallation of oxazoline ligand *(1S,2R)*-**7a** with $[RhCp^*Cl_2]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$ was undertaken. These complexes were then tested for the asymmetric hydrogenation of imine **9**, which was used as a model substrate for the optimisation of conditions (Scheme 4.8). As can be seen, the enantioselectivity obtained previously with Ir-oxazoline complex was not surpassed: Only 23% *ee* was obtained with the analogous Rh-oxazoline complex. In the case of the ruthenium, the cyclometallated complex was not even formed and only decomposition took place.




**Scheme 4.8**: Metal effect on asymmetric hydrogenation of **9**.

As previously mentioned, chiral imidazolidine ligands were also tested on the asymmetric hydrogenation of **9**. These catalysts were previously tested for ATH of imines by a different member of the group.[41] The results are presented in Scheme 4.9. Lower enantioselectivity was obtained when the unsubstituted imidazolidine **11** was used as the ligand, compared to the unsubstituted oxazoline **7a** (15% *vs* 45% *ee*). A more promising result was obtained with disubstituted imidazolidine **12** (53% *ee*). It is worth noting that this ligand provides better enantioselectivity under hydrogenation conditions than transfer hydrogenation conditions, where only 33% *ee* was obtained.[41] In the hope to increase the enantioselectivity, a substituent was introduced on one of the nitrogen atoms of the imidazolidine ligand. Disappointingly, ligand **13** gave a practically racemic mixture for the hydrogenation of **9** (3% *ee*).




**Scheme 4.9**: Imidazolidine ligands for the asymmetric hydrogenation of **9**.

Although a promising result was obtained with **12**, it was decided to focus the study on the oxazoline ligands. In contrast to oxazolines (*vide supra*), in the cyclometallation of imidazolidines with $[IrCp^*Cl_2]_2$, three different isomers were observed by $^1H$ NMR, although mass spectrometry only shows one value. This is due to cyclometallation at the phenyl ring from the aldehyde and at one of the phenyl rings from the diamine moiety (Figure 4.3). Therefore, it is more difficult to determine which one of the three complexes formed is the active and enantioselective species.

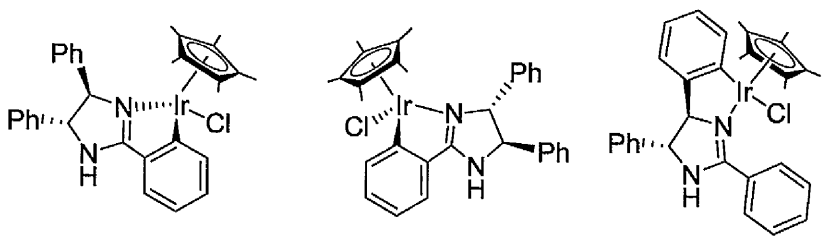
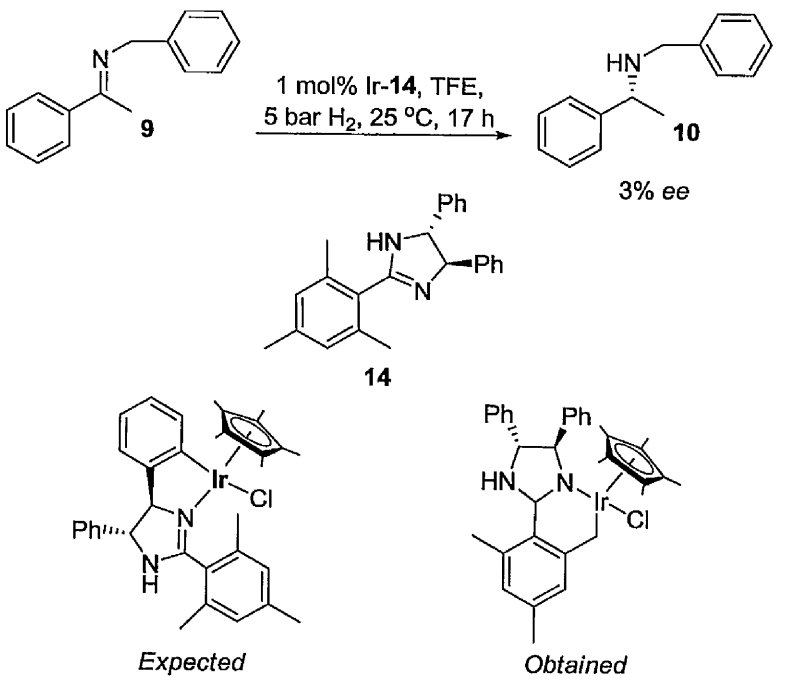


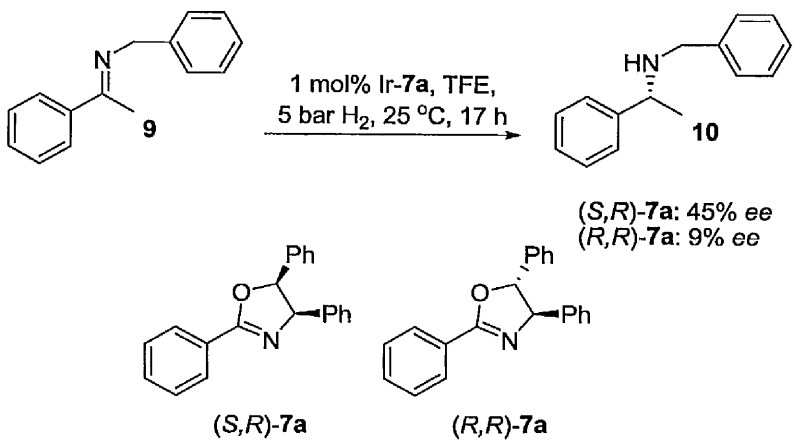
**Figure 4.3**: Isomers observed in cyclometallated chiral Ir-imidazolidine complexes.

However, before turning our attention exclusively to oxazoline ligands, we tested the chiral imidazolidine **14** for the Ir-catalysed asymmetric hydrogenation of **9**. This ligand would force the cyclometallation into one of the phenyl rings of the diamine moiety. This could help us to determine if this third isomer is the key to obtain high enantioselectivity. Unfortunately, the catalyst turned black when TFE was added, and only 3% *ee* was obtained (Scheme 4.10). X-ray diffraction finally showed that cyclometallation actually took place on one of the methyl groups, instead of the phenyl ring from the diamine side (Scheme 4.10). The low enantioselectivity could thus be due to dissociation of **14** from the iridium following protonolysis of the Ir-C bond.




**Scheme 4.10:** Asymmetric hydrogenation of **9** with Ir-**14**.

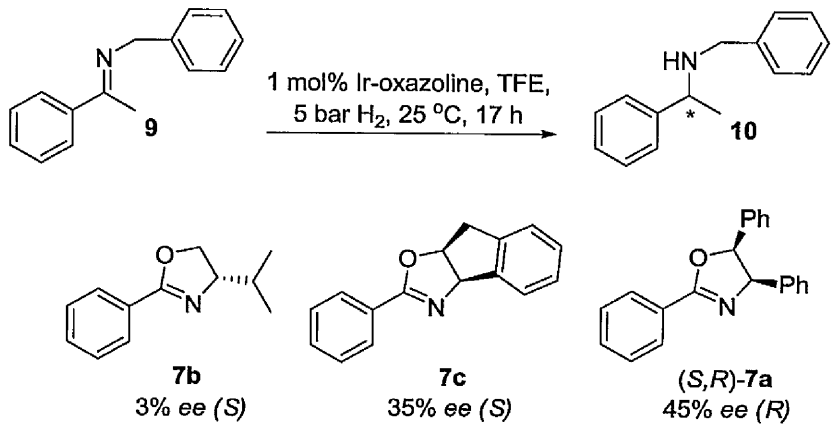
Most of the oxazoline ligands **7** contain two stereogenic centres, leading to two diastereoisomers. For this reason, we compared the enantioselectivity between (*R,R*)-**7a** and (*S,R*)-**7a** ligands for the hydrogenation of **9** (Scheme 4.11). (*S,R*)-**7a** showed to be superior, leading to 45% *ee* compared to 9% *ee* obtained with (*R,R*)-**7a**. Crystals of Ir-(*S,R*)-**7a** and Ir-(*R,R*)-**7a** for X-ray diffraction experiments were obtained by other member of the group.[41] It is worth noting that the X-ray diffraction shows that the diastereomeric ratio of Ir-(*R,R*)-**7a** was 1:1, while the diastereomeric ratio of Ir-(*S,R*)-**7a** was 2:1. These observations suggests that a high diastereomeric ratio is required in order to obtain high enantioselectivity.




**Scheme 4.11**: Effect of ligand configuration on the hydrogenation of **9**.

The effect of the amino alcohol moiety was also studied by comparing oxazoline ligands derived from different amino alcohols. The results are shown in Scheme 4.12. The bulkiness has a dramatic effect on the enantioselectivity. Only 3% *ee* was obtained with oxazoline **7b**, derived from *L*-valinol. A better enantioselectivity of 35% *ee* was obtained with the bulkier oxazoline **7c**,

although it did not surpass the initial enantioselectivity of 45% *ee* with (*S,R*)-**7a** (Scheme 4.12). It is also noteworthy that product of *S*-configuration was obtained with ligands **7b** and **7c**, while *R*-configuration was obtained with every oxazoline ligand derived from *(1S, 2R)*-2-amino-1,2-diphenylethanol.

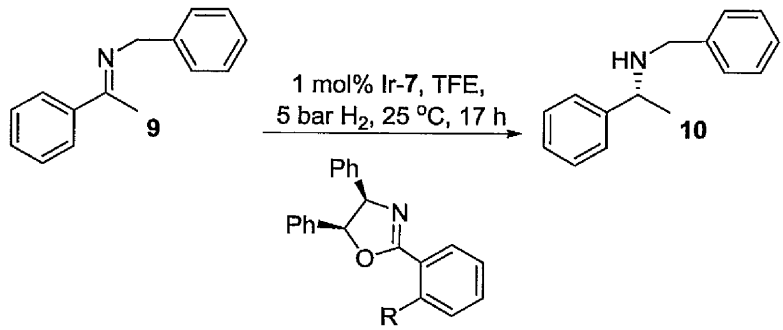



**Scheme 4.12:** Effect of aminoalcohol on asymmetric hydrogenation of **9**.

The substitution at the *ortho*-position of the aldehyde was subsequently studied (Table 4.1). The presence of a substituent on the 2-position had a positive effect on the enantioselectivity (entry 1 *vs* 2-6). Moving on to electron-donating substituents, bulkiness seemed to improve the enantioselectivity (entries 5 *vs* 6). These results prompted us to synthesise an oxazoline ligand with an *i*Pr substituent at the *ortho*-positon. Unfortunately, almost a racemic mixture was obtained (entry 7). The diastereoselectivity on the cyclometallated complexes with ligands **7h** and **7i** increases from 2.6:1 to 4:1, respectively. We rationalise that the complex providing the lowest enantioselectivity for the hydrogenation of **9** increased in proportion. An example of oxazoline derived from 3-substitued aldehyde was also studied

(entry 8). This oxazoline has two inequivalent positions for cyclometallation, leading to four possible isomers. This situation makes it very difficult to determine the most selective catalyst.

**Table 4.1**: Effect of *ortho*- and *meta*-substitution at the oxazoline ligand on the enantioselectivity of hydrogenation of **9**.[a]



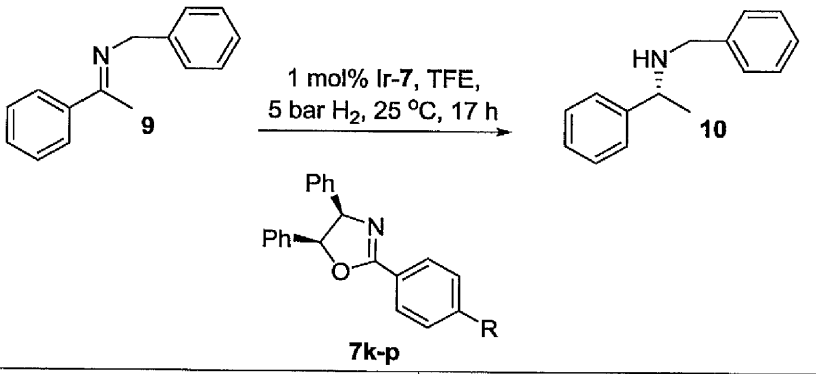

**7a,d-i**

| Entry | Ligand | R | *ee* (%) | Entry | Ligand | R | *ee* (%) |
|---|---|---|---|---|---|---|---|
| 1 | **7a** | H | 45 | 5 | **7g** | OMe | 19 |
| 2 | **7d** | Cl | 57 | 6 | **7h** | Me | 66 |
| 3 | **7e** | Br | 63 | 7 | **7i** | *i*Pr | 8 |
| 4 | **7f** | Ph | 56 | 8[b] | **7j** | Me | 56 |

[a]0.25 mmol **9**, 2.5 μmol catalyst, 4 mL TFE, 5 bar $H_2$, 25 °C, 17 hours; Full conversion for all the reactions. [b]Oxazoline derived from *m*-methylbenzaldehyde.

In addition to the *ortho*- and *meta*-substituents, oxazolines derived from *para*-substituted benzaldehydes were also studied (Table 4.2). Electron-donating substituents showed better enantioselectivities (entry 1 *vs* 2-6). Within electron-donating substituents, the increase in bulkiness had a positive effect on the enantioselectivity. With *i*Pr and *t*Bu substituents, the enantioselectivity reached a maximum of ~71% *ee* (entries 4 and 5). There was a clear need for a much bulkier oxazoline to boost the enantioselectivity.

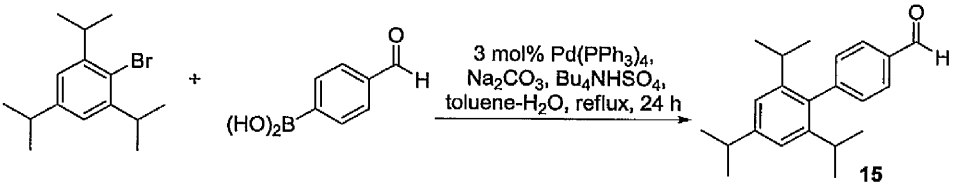
**Table 4.2**: Effect of *para*-substitution at the oxazoline ligand on the enantioselectivity of hydrogenation of **9**.[a]




| Entry | Ligand | R | *ee* (%) | Entry | Ligand | R | *ee* (%) |
|---|---|---|---|---|---|---|---|
| 1 | **7k** | $CF_3$ | 45 | 4 | **7n** | *i*Pr | 71 |
| 2 | **7l** | OMe | 55 | 5 | **7o** | *t*Bu | 70 |
| 3 | **7m** | Me | 55 | 6 | **7p** | R[b] | 78 |

[a]Same reactions conditions as those in Table 4.1. [b] R: 2,4,6-(2-$C_3H_7$)$_3$-$C_6H_2$.

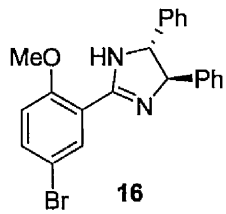
A diaryl benzaldehyde could lead to a bulkier chiral oxazoline. We, therefore, decided to synthesise aldehyde **15**, by Suzuki coupling (Scheme 4.13).[42] The corresponding oxazoline **7p** was then synthesised, cyclometallated and tested for hydrogenation of **9**. Delightfully, the enantioselectivity increased to 78% *ee* (Table 4.2, entry 6).




**Scheme 4.13**: Synthesis of aldehyde **15** by Suzuki coupling.

Given this finding and the positive effect noted in Table 4.1, we then studied the effect of disubstitution at the oxazoline ligand on the

enantioselectivity. Ligand **16** had previously proved to be one of the most effective imidazolidine ligands for ATH with Ir-cyclometallated complex (Figure 4.4).[41] Prompted by this, we decided to synthesise and test **7q** first, an oxazoline analogue of **16** (Figure 4.4). Unfortunately, only 12% *ee* was obtained (Table 4.3, entry 1). It is worth noting that for ligand **7q**, cyclometallation is observed in two different phenyl rings, resulting in 3 different isomers (see Figure 4.3). This is probably due to steric effects on the phenyl ring from the aldehyde.

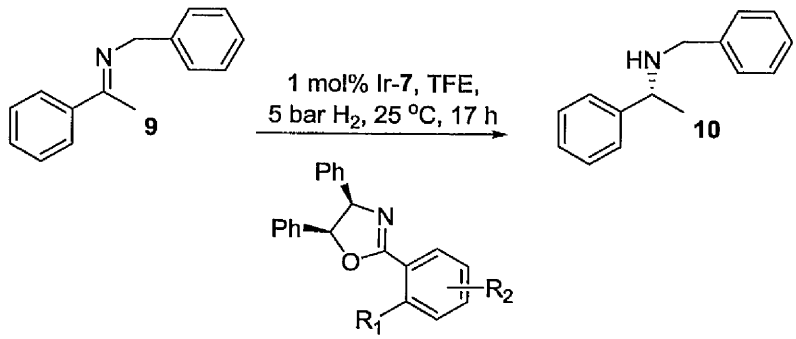



**16**

**Figure 4.4:** Imidazolidine ligand applied for ATH of imines with cyclometallated Ir-complex.

On the other hand, we presumed that a synergistic effect could take place with a 2,4-disubstitued benzaldehyde, where both substituents would boost the enantioselectivity. Indeed, the combination of *o*-Br and *p*-Me substituents increased the enantioselectivity up to 69% *ee*, from 63 and 55% *ee* for the mono-substitution, respectively (Table 4.3, entries 2 and 3 *vs* 4). This improvement on the enantioselectivity indicates that the combination of the two best substituents, *o*-Me and *p*-triisopropylphenyl would be very promising.

**Table 4.3**: Effect of disubstitution on the oxazoline ligand on the enantioselectivity of hydrogenation of **9**.

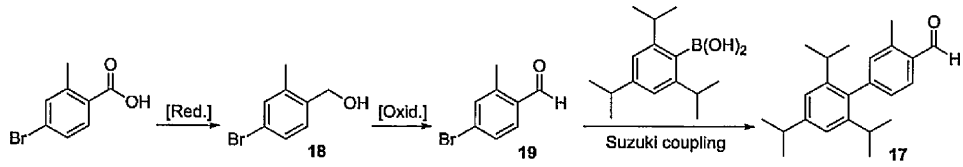



**7e,m,p,r**

| Entry[a] | Ligand | $R_1$ | $R_2$ | *ee* (%) |
|---|---|---|---|---|
| 1 | **7q** | OMe | 5-Br | 12 |
| 2 | **7e** | Br | 4-H | 63 |
| 3 | **7m** | H | 4-Me | 55 |
| 4 | **7r** | Br | 4-Me | 69 |

[a]Same reactions conditions as those in Table 4.1.

Therefore, we synthesised aldehyde **17**, following the procedure shown in Scheme 4.14. The corresponding oxazoline was then synthesised, cyclometallated and the catalyst tested for the hydrogenation of **9**. Unfortunately, only few milligrams of the complex were obtained and some impurities were observed by $^1$H NMR; the crystallization (i.e. purification) of the catalyst became very difficult. The enantioselectivity obtained was only 42% *ee*. This could be due to the impurities present in the solid.




**Scheme 4.14**: Synthesis of aldehyde **17** by Suzuki coupling.

## 4.3 Conclusion and future work

We have described the efforts to develop a chiral cyclometallated Ir-oxazoline catalyst for asymmetric hydrogenation of imines. It is the first time that this type of catalyst has been synthesised and applied for asymmetric hydrogenation. A promising 78% enantiomeric excess was obtained with ligand **7p**. Future work should focus on the synthesis of bulkier chiral oxazoline ligands and expand the scope to other *N*-alkyl imines.

## 4. 4 Experimental

### General procedure for the synthesis of oxazoline ligands[39]

A Schlenk tube was charged with 4 Å MS (1 g), an amino alcohol (1 mmol) and an aldehyde (1 mmol), followed by degassing with $N_2$ three times. Distilled DCM was then added. The mixture was stirred for 14 hours at room temperature. NBS was then added and the mixture was further stirred for 2 hours. The mixture was filtered through celite and washed with saturated $NaHCO_{3(aq)}$ solution (4 × 10 mL) and $H_2O$ (1 × 10 mL). The organic layer was dried over $MgSO_4$, filtered through celite and concentrated to afford the crude product. Flash chromatography purification with a column of silica gel eluted

with petroleum ether/ethyl acetate (20/1 to 10/1) yielded the desired oxazoline product.

**General procedure for the synthesis of cyclometallated complexes**[36-37,43]

An oven-dried Schlenk tube containing a stir bar was charged with $[IrCp^*Cl_2]_2$ (1 eq), an oxazoline ligand (2 eqs) and NaOAc (10 eqs.). Following degassing three times, freshly distilled DCM was injected. The resulting mixture was stirred at room temperature overnight. The reaction mixture was then filtered through celite and concentrated *in vacuo*. The resulting solid was washed with diethyl ether/hexane and used for imine hydrogenation without further purification.

**General procedure for the hydrogenation of imine 9**

To a glass liner equipped with a stir bar was added **9** (0.25 mmol), catalyst (2.5 μmol) and TFE (4 mL). The glass liner was then placed into an autoclave, followed by degassing with $H_2$ three times. The hydrogenation was carried out at 5 bar $H_2$ with stirring at 25 °C for 15 hours. The hydrogen gas was then carefully released in a fume hood and the solution was filtered, transferred to a flask, and concentrated to afford the crude product. 1H NMR showed full conversion for all the reactions. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (20/1 to 5/1) yielded the desired amine product.

**Procedure for the synthesis of aldehydes 15 and 17[42]**

An oven-dried Schlenk tube containing a stir bar was charged with boronic acid (1.2 eq), aryl halide (1 eq) and $Bu_4NHSO_4$ (0.1 eq). Following degassing three times, $Pd(PPh_3)_4$ (0.03 eq) was then added. The Schlenk tube was degassed again 3 times. Freshly distilled toluene was injected (10 mL), followed by $Na_2CO_{3(aq)}$ (2 M, 6 mL). The reaction was then carried out at 110 °C for 24 hours under a $N_2$ atmosphere. The mixture was extracted with ethyl acetate, and the organic layer was dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*. Flash chromatography purification with a column of silica gel eluted with petroleum ether/DCM (5/1 to 0/1) yielded the desired aldehyde product.

**Procedure for the synthesis of alcohol 18**

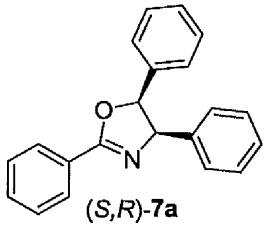
An oven-dried two-necked flask containing a stir bar was charged with 4-bromo-2-methylbenzoic acid (3.2 g, 15 mmol). It was then connected to a reflux condenser and degassed three times. THF (20 mL) was added. $NaBH_4$ (680 mg, 18 mmol) was then added in small portions. $H_2$ evolution occurred for approximately 10 min. After $H_2$ evolution stopped, the reaction temperature was set up at 65 °C for 17 hours under $N_2$ atmosphere. The mixture was then cooled to room temperature and washed with saturated $NaHCO_{3(aq)}$, and then extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*. The product was used in the following step without further purification.

**Procedure for the synthesis of aldehyde 19**

An oven-dried Schlenk tube containing a stir bar was charged with pyridinium chlorochromate (PCC) (1.51 g, 7 mmol). It was then connected to a pressure-equalising dropping funnel and degassed three times. The funnel was then charged with a solution of **18** (1.2 g, 6 mmol) in THF (10 mL), which was added slowly into the Schlenk tube. The reaction mixture was left stirring overnight at room temperature under $N_2$ atmosphere. The reaction mixture was then filtered through celite, and concentrated *in vacuo*. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (15/1 to 10/1) yielded **19**.

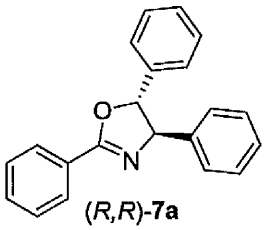
## 4.5 Analytical data

Compounds **7d-s**, **17** and **19** are new compounds.



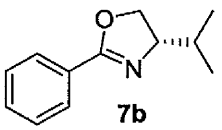

(*S,R*)-**7a**

(*4R,5S*)-2,4,5-Triphenyl-4,5-dihydrooxazole.[41] The product (254 mg, 85% yield) was obtained as a white solid according to the general procedure;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.68 (d, $J$ = 10.1 Hz, 1H), 5.96 (d, $J$ = 10.1 Hz, 1H), 6.85-6.90 (m, 4H), 6.93-7.02 (m, 6H), 7.41-7.45 (m, 2H), 7.48-7.53 (m, 1H), 8.11 (dd, $J$ = 8.3, 1.2 Hz, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 74.9, 85.7, 126.7, 127.4, 127.8, 128.0(1), 128.0(7), 128.1(1), 128.3, 128.9(6), 129.0(1), 132.2, 137.0, 138.1, 165.4;
**HRMS** for $C_{21}H_{18}NO$ $[M+H]^+$: Calcd: 300.1388; Found: 300.1389;
**Anal Calcd** for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.58. Found: C, 84.27; H, 5.82; N, 4.34.



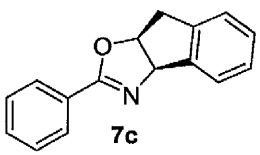
(*R,R*)-**7a**

(*4R,5R*)-2,4,5-Triphenyl-4,5-dihydrooxazole.[39,44] The product (245 mg, 82% yield) was obtained as a white solid according to the general procedure;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.22 (d, $J$ = 7.6 Hz, 1H), 5.41 (d, $J$ = 7.6 Hz, 1H), 7.29-7.56 (m, 13H), 8.13-8.15 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 79.5, 89.4, 126.1, 127.2, 127.9, 128.2, 128.8, 128.9, 129.1, 129.3, 129.4, 132.1, 140.9, 142.2, 164.5;
**HRMS** for $C_{21}H_{18}NO$ $[M+H]^+$: Calcd: 300.1388; Found: 300.1385;
**Anal Calcd** for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.58. Found: C, 84.60; H, 5.77; N, 4.58.



**7b**

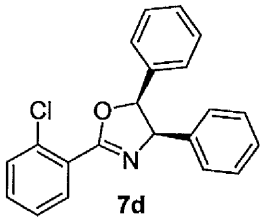
(*S*)-4-Isopropyl-2-phenyl-4,5-dihydrooxazole.[39] The product (132 mg, 70% yield) was obtained as a colourless oil according to the general procedure;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 0.93 (d, $J$ = 6.8 Hz, 3H), 1.03 (d, $J$ = 6.8 Hz, 3H), 1.87 (septetd, $J$ = 6.8, 1.6 Hz, 1H), 4.07-4.16 (m, 2H), 4.41 (td, $J$ = 7.2, 1.6 Hz, 1H), 7.38-7.42 (m, 2H), 7.44-7.49 (m, 1H), 7.94-7.97 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 18.5, 19.4, 33.2, 70.5, 73.0, 128.4, 128.6, 128.7, 131.6, 163.7;
**HRMS** for $C_{12}H_{16}NO$ $[M+H]^+$: Calcd: 190.1226; Found: 190.1224;
**Anal Calcd** for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.73; H, 8.16; N, 7.44.



**7c**

(*3aR,8aS*)-2-Phenyl-8,8a-dihydro-3aH-indeno[1,2-d]oxazole.[39,45] The product (179 mg, 76% yield) was obtained as a white solid according to the general procedure;
**Mp** = 114-116 °C
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.36 (dd, $J$ = 17.0, 1.4 Hz, 1H), 3.50 (dd, $J$ = 17.0, 6.7 Hz, 1H), 5.48 (ddd, $J$ = 8.0, 6.7, 1.4 Hz, 1H), 5.74 (d, $J$ = 8.0 Hz, 1H), 7.25-7.30 (m, 3H), 7.34-7.38 (m, 2H), 7.41-7.45 (m, 1H), 7.56-7.58 (m, 1H), 7.91-7.94 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 40.2, 77.4, 83.6, 125.7, 126.0, 127.9, 128.2, 128.6, 128.7, 128.9, 131.7, 140.1, 142.4, 164.4;
**HRMS** for $C_{14}H_{16}NO$ $[M+H]^+$: Calcd: 214.1226; Found: 214.1227;

**Anal Calcd** for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 79.84; H, 5.54; N, 5.55.




**7d**

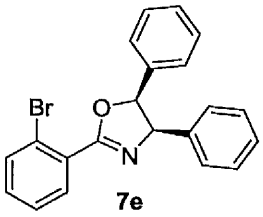
(*4R,5S*)-2-(2-Chlorophenyl)-4,5-diphenyl-4,5-dihydrooxazole. The product (176 mg, 53% yield) was obtained as a white solid according to the general procedure;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.80 (d, $J$ = 10.2 Hz, 1H), 6.06 (d, $J$ = 10.2 Hz, 1H), 6.98-7.11 (m, 10H), 7.39 (td, $J$ = 7.6, 1.3 Hz, 1H), 7.46 (td, $J$ = 7.6, 1.8 Hz, 1H), 7.55 (dd, $J$ = 7.6, 1.3 Hz, 1H), 8.01 (dd, $J$ = 7.6, 1.8 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 75.1, 86.0, 126.9, 127.1, 127.4, 127.6, 127.9, 128.0(8), 128.1(2), 128.3, 131.4, 132.1, 132.3, 134.2, 136.6, 137.8, 164.1;

**HRMS** for $C_{21}H_{17}ClNO$ $[M+H]^+$: Calcd: 334.0999; Found: 334.1007;

**Anal Calcd** for $C_{21}H_{16}ClNO$: C, 75.56; H, 4.83; N, 4.20. Found: C, 75.57; H, 4.95; N, 4.62.




**7e**

(*4R,5S*)-2-(2-Bromophenyl)-4,5-diphenyl-4,5-dihydrooxazole. The product (189 mg, 50% yield) was obtained as a white solid according to the general procedure;

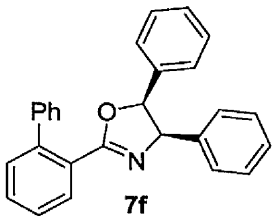
**Mp** = 95-97 °C

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.80 (d, $J$ = 10.3 Hz, 1H), 6.07 (d, $J$ = 10.3 Hz, 1H), 7.00-7.10 (m, 10H), 7.37 (td, $J$ = 7.7, 1.8 Hz, 1H), 7.44 (td, $J$ = 7.7, 1.3 Hz, 1H), 7.75 (dd, $J$ = 7.7, 1.3 Hz, 1H), 7.96 (dd, $J$ = 7.7, 1.8 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 75.1, 86.1, 122.5, 127.0, 127.4, 127.7, 127.9, 128.0(7), 128.1(2), 128.3, 129.8, 132.2, 132.4, 134.6, 136.6, 137.8, 164.7;

**HRMS** for $C_{21}H_{17}{}^{79}BrNO_2$ $[M+H]^+$: m/z Calcd: 378.0494; Found: 378.0490;

**Anal Calcd** for $C_{21}H_{16}BrNO$: C, 66.68; H, 4.26; N, 3.70. Found: C, 66.00; H, 4.31; N, 3.52.




**7f**

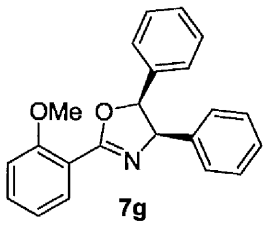
(*4R,5S*)-2-(Biphenyl-2-yl)-4,5-diphenyl-4,5-dihydrooxazole. The product (105 mg, 28% yield) was obtained as a white solid according to the general procedure;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.58 (d, $J$ = 10.3 Hz, 1H), 5.65 (d, $J$ = 10.3 Hz, 1H), 6.62-6.65 (m, 2H), 6.79-6.81 (m, 2H), 6.93-6.97 (m, 3H), 6.99-7.01 (m, 3H), 7.37-7.46 (m, 4H), 7.48-7.53 (m, 3H), 7.57 (td, $J$ = 7.6, 1.3 Hz, 1H), 8.02 (d, $J$ = 7.8 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 74.2, 85.6, 125.8, 126.3, 126.8, 127.1, 127.3, 127.4, 127.5, 127.7, 127.9, 128.1, 128.3, 128.8, 130.3, 130.6, 136.7, 137.8, 141.5, 142.3, 166.5;

**HRMS** for $C_{27}H_{22}NO$ $[M+H]^+$: Calcd: 376.1701; Found: 376.1716;

**Anal Calcd** for $C_{27}H_{21}NO$: C, 86.37; H, 5.64; N, 3.73. Found: C, 86.41; H, 5.62; N, 3.54.




**7g**

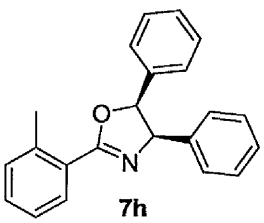
(*4R,5S*)-2-(2-Methoxyphenyl)-4,5-diphenyl-4,5-dihydrooxazole. The product (168 mg, 51% yield) was obtained as a white solid according to the general procedure;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 5.76 (d, $J$ = 10.2 Hz, 1H), 5.98 (d, $J$ = 10.2 Hz, 1H), 6.96-7.06 (m, 12H), 7.48 (td, $J$ = 7.9, 1.8 Hz, 1H), 7.96 (dd, $J$ = 7.9, 1.8 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 56.1, 74.8, 84.8, 111.9, 117.2, 120.4, 126.5, 126.8, 127.3, 127.5, 127.6, 128.0, 131.5, 132.6, 136.8, 137.9, 158.9, 163.9;

**HRMS** for $C_{20}H_{20}NO_2$ $[M+H]^+$: Calcd: 330.1494; Found: 330.1495;

**Anal Calcd** for $C_{22}H_{19}NO_2$ + ½$H_2O$: C, 70.08; H, 5.96; N, 4.14. Found: C, 78.08; H, 5.96; N, 3.96.

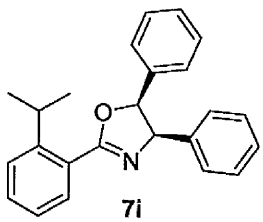



**7h**

(*4R,5S*)-4,5-Diphenyl-2-(o-tolyl)-4,5-dihydrooxazole. The product (147 mg, 47% yield) was obtained as a white solid according to the general procedure;

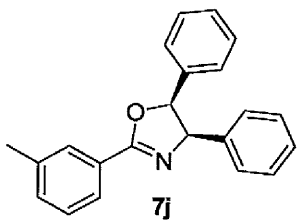
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 5.72 (d, $J$ = 10.2 Hz, 1H), 5.91 (d,

$J$ = 10.2 Hz, 1H), 6.88-6.92 (m, 4H), 6.94-7.00 (m, 6H), 7.22-7.27 (m, 2H), 7.35 (td, $J$ = 7.5, 1.2 Hz, 1H), 8.01 (dd, $J$ = 7.8, 1.2 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 25.8, 77.8, 84.6, 125.2, 126.4, 126.8, 126.9, 127.3, 127.6, 127.7, 127.9, 130.3, 136.8, 137.9, 139.4(6), 139.5(2), 139.9, 165.4;
**HRMS** for $C_{22}H_{20}NO$ $[M+H]^+$: Calcd: 314.1545; Found: 314.1552.
**Anal Calcd** for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.20; H, 5.96; N, 4.06.



**7i**

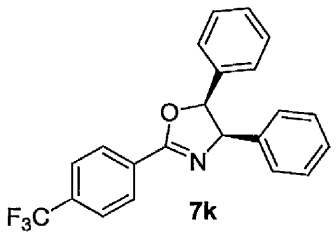
(*4R,5S*)-2-(2-Isopropylphenyl)-4,5-diphenyl-4,5-dihydrooxazole. The product (133 mg, 39% yield) was obtained as a white solid according to the general procedure;
**Mp** = 80-83 °C
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.32 (d, $J$ = 6.8 Hz, 6H), 4.15 (septet, $J$ = 6.8 Hz, 1H), 5.78 (d, $J$ = 10.2 Hz, 1H), 6.00 (d, $J$ = 10.2 Hz, 1H), 6.96-6.99 (m, 4H), 7.00-7.08 (m, 6H), 7.27-7.32 (m, 1H), 7.49-7.50 (m, 2H), 7.98 (d, $J$ = 7.6 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 29.0, 30.2, 75.1, 86.0, 126.2(7), 126.3(1), 126.4, 126.9, 127.4, 127.6(7), 127.7(1), 127.9, 130.3, 131.9, 136.7, 137.9, 149.7, 149.8, 165.7;
**IR** (neat) 2977 (s), 2360 (m), 1635 (m), 1385 (m), 1153 (m), 1041 (m), 964 (m), 760 (m), 694 (s) $cm^{-1}$;
**HRMS** for $C_{24}H_{24}NO$ $[M+H]^+$: Calcd: 342.1858; Found: 342.1862;
**Anal Calcd** for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.41; H, 6.82; N, 3.91.



**7j**

(*4R,5S*)-4,5-Diphenyl-2-m-tolyl-4,5-dihydrooxazole. The product (191 mg, 61% yield) was obtained as a white solid according to the general procedure;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 5.74 (d, $J$ = 10.1 Hz, 1H), 6.02 (d, $J$ = 10.1 Hz, 1H), 6.92-6.98 (m, 4H), 7.01-7.40 (m, 6H), 7.39 (d, $J$ = 5.8 Hz, 2H), 7.96-7.98 (m, 1H), 8.02 (s, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.3, 74.4, 85.3, 127.7, 126.4, 127.0, 127.3, 127.4, 127.6(6), 127.7(0), 127.9, 128.5, 129.2, 132.6, 136.6, 137.7, 138.4, 165.2;
**HRMS** for $C_{22}H_{22}NO$ $[M+H]^+$: Calcd: 314.1545; Found: 314.1545;

**Anal Calcd** for $C_{22}H_{19}NO + H_2O$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.45; H, 6.08; N, 4.47.



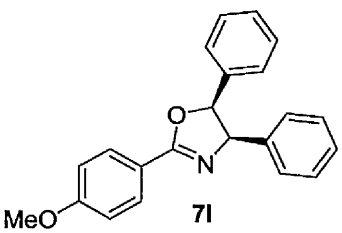
**7k**

(*4R,5S*)-4,5-Diphenyl-2-(4-(trifluoromethyl)phenyl)-4,5-dihydrooxazole. The product (191 mg, 52% yield) was obtained as a white solid according to the general procedure;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.79 (d, $J$ = 10.2 Hz, 1H), 6.07 (d, $J$ = 10.2 Hz, 1H), 6.91-6.96 (m, 4H), 7.03-7.09 (m, 6H), 7.77 (d, $J$ = 8.2 Hz, 2H), 8.30 (d, $J$ = 8.2 Hz, 2H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 74.5, 85.7, 122.4, 125.6, 126.3, 127.2, 127.6, 127.8, 128.4 (q, $J_{CF}$ = 3.2 Hz), 129.0, 130.8, 133.4 (q, $J_{CF}$ = 33.3 Hz), 136.2, 137.2, 163.8 (The carbon resonance $CF_3$ was not observed, possibly due to overlap with other aromatic carbon resonances);

**HRMS** for $C_{22}H_{17}F_3NO$ $[M+H]^+$: Calcd: 368.1262; Found: 368.1274.



**7l**

(*4R,5S*)-2-(4-Methoxyphenyl)-4,5-diphenyl-4,5-dihydrooxazole. The product (197 mg, 60% yield) was obtained as a white solid according to the general procedure;

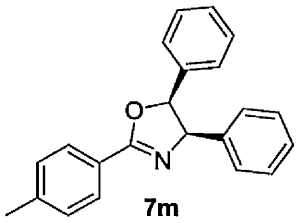
**Mp** = 114-118 °C

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 5.72 (d, $J$ = 9.8 Hz, 1H), 6.00 (d, $J$ = 9.8 Hz, 1H), 6.92-6.97 (m, 4H), 6.98-7.08 (m , 8H), 8.10-8.14 (m, 2H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 55.9, 74.8, 85.6, 114.3, 120.3, 126.7, 127.3, 127.7, 128.0, 128.1, 128.3, 130.8, 137.1, 138.3, 162.9, 165.1;

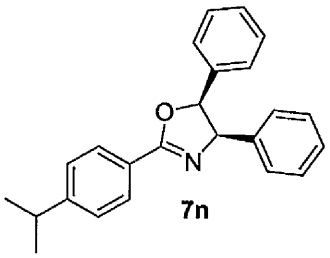
**HRMS** for $C_{22}H_{20}NO_2$ $[M+H]^+$: Calcd: 330.1494; Found: 330.1495;

**Anal Calcd** for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 79.53; H, 5.81; N, 4.08.



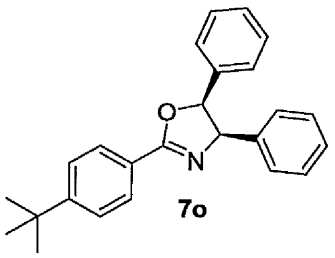
**7m**

(*4R,5S*)-4,5-Diphenyl-2-p-tolyl-4,5-dihydrooxazole. The product (222 mg, 71% yield) was obtained as a white solid according to the general procedure;
**Mp** = 162-165 °C
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 5.73 (d, $J$ = 10.0 Hz, 1H), 6.01 (d, $J$ = 10.0 Hz, 1H), 6.92-6.97 (m, 4H), 7.00-7.07 (m, 6H), 7.31 (d, $J$ = 8.1 Hz, 2H), 8.07 (d, $J$ = 8.1 Hz, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 22.1, 74.9, 85.6, 125.1, 126.7, 127.3, 127.8, 128.0, 128.1, 128.3, 129.0, 129.7, 137.1, 138.2, 142.7, 165.4;
**HRMS** for $C_{22}H_{20}NO$ $[M+H]^+$: Calcd: 314.1545; Found: 314.1547;
**Anal Calcd** for $C_{22}H_{19}NO + ½H_2O$: C, 81.96; H, 6.25; N, 4.34. Found: C, 81.84; H, 6.00; N, 4.09.



**7n**

(*4R,5S*)-2-(4-Isopropylphenyl)-4,5-diphenyl-4,5-dihydrooxazole. The product (235 mg, 69% yield) was obtained as a white solid according to the general procedure;
**Mp** = 133-137 °C
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.24 (d, $J$ = 6.9 Hz, 6H), 2.93 (septet, $J$ = 6.9 Hz, 1H), 5.67 (d, $J$ = 10.0 Hz, 1H), 5.94 (d, $J$ = 10.0 Hz, 1H), 6.84-6.90 (m, 4H), 6.93-7.01 (m, 6H), 7.29 (d, $J$ = 8.2 Hz, 2H), 8.03 (d, $J$ = 8.2 Hz, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 24.2, 34.7, 74.8, 85.6, 125.4, 126.7, 127.1, 127.3, 127.8, 128.0, 128.1, 128.3, 129.1, 137.1, 138.2, 153.5, 165.4;
**HRMS** for $C_{24}H_{24}NO$ $[M+H]^+$: Calcd: 342.1858; Found: 342.1865;
**Anal Calcd** for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.06; H, 6.83; N, 3.91.



**7o**

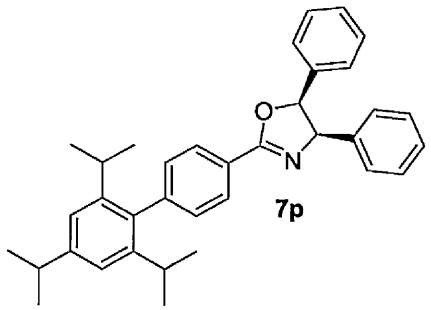
(*4R,5S*)-2-(*4-tert*-Butylphenyl)-4,5-diphenyl-4,5-dihydrooxazole. The product (248 mg, 70% yield) was obtained as a white solid according to the general procedure;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 5.67 (d, $J$ = 10.0 Hz, 1H), 5.94 (d, $J$ = 10.0 Hz, 1H), 6.84-6.92 (m, 4H), 6.93-7.02 (m, 6H), 7.44-7.47 (m, 2H), 8.03-8.06 (m, 2H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 13.6, 35.5, 74.9, 85.6, 125.0, 125.9, 126.7, 127.3, 127.7, 128.0, 128.1, 128.3, 128.8, 137.1, 138.2, 155.7, 165.4;

**HRMS** for $C_{25}H_{26}NO$ $[M+H]^+$: Calcd: 356.2010; Found: 356.2014;

**Anal Calcd** for $C_{25}H_{15}NO$: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.54; H, 7.18; N, 3.85.



**7p**

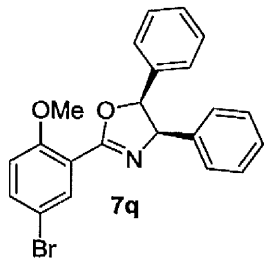
(*4R,5S*)-4,5-Diphenyl-2-(2',4',6'-triisopropylbiphenyl-4-yl)-4,5-dihydrooxazole. The product (73 mg, 15% yield) was obtained as a white solid according to the general procedure;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.04 (d, $J$ = 6.9 Hz, 12H), 1.25 (d, $J$ = 6.9 Hz, 6H), 2.56 (septet, $J$ = 6.9 Hz, 2H), 2.89 (septet, $J$ = 6.9 Hz, 1H), 5.71 (d, $J$ = 10.1 Hz, 1H), 5.98 (d, $J$ = 10.1 Hz, 1H), 6.90-7.04 (m, 12H), 7.26 (d, $J$ = 8.3 Hz, 2H), 8.13 (d, $J$ = 8.3 Hz, 2H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 24.1, 24.2, 30.3, 34.3, 74.5, 85.3, 120.6, 125.7, 126.4, 127.0, 127.4, 127.6(6), 127.7(1), 127.9, 128.2, 130.1, 136.2, 136.6, 137.8, 145.0, 146.3, 148.3, 165.1;

**HRMS** for $C_{36}H_{40}NO$ $[M+H]^+$: Calcd: 502.3110; Found: 502.3120;

**Anal Calcd** for $C_{36}H_{39}NO$: C, 86.18; H, 7.84; N, 2.79. Found: C, 86.25; H, 8.10; N, 2.50.




**7q**

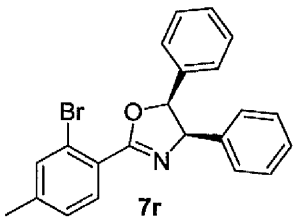
(*4R,5S*)-2-(2-Bromo-5-methoxyphenyl)-4,5-diphenyl-4,5-dihydrooxazole. The product (194 mg, 48% yield) was obtained as a white solid according to the general procedure;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 5.77 (d, $J$ = 10.2 Hz, 1H), 5.99 (d, $J$ = 10.2 Hz, 1H), 6.93-7.10 (m, 11H), 7.59 (dd, $J$ = 8.9, 2.6 Hz, 1H); 8.08 (d, $J$ = 2.6 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 56.8, 75.2, 85.4, 112.9, 114.1, 119.3, 126.9, 127.3, 127.8, 128.0, 128.1, 128.3, 134.4, 135.6, 136.9, 138.0, 158.4, 163.0;

**HRMS** for $C_{22}H_{18}{}^{79}BrNO_2$ $[M+H]^+$: Calcd: 408.0599; Found: 408.0618;

**Anal Calcd** for $C_{22}H_{17}BrNO_2$: C, 64.72; H, 4.44; N, 3.43. Found: C, 64.79; H, 4.43; N, 3.33.



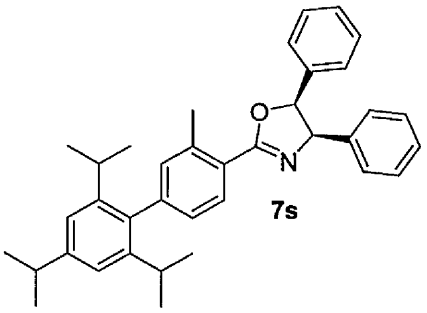

**7r**

(*4R,5S*)-2-(2-bromo-4-methylphenyl)-4,5-diphenyl-4,5-dihydrooxazole. The product (39 mg, 10% yield) was obtained as a translucent oil according to the general procedure;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 5.70 (d, $J$ = 10.3 Hz, 1H), 5.96 (d, $J$ = 10.3 Hz, 1H), 6.92-7.01 (m, 10H), 7.15 (dd, $J$ = 7.9, 0.8 Hz, 1H), 7.50 (d, $J$ = 0.8 Hz, 1H), 7.79 (d, $J$ = 7.9 Hz, 1H);

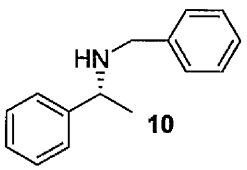
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 21.1, 74.7, 85.6, 121.9, 126.3, 126.6, 127.0, 127.4, 127.6, 127.7, 127.9, 128.1, 131.6, 134.8, 136.3, 137.5, 142.8, 164.3;

**HRMS** for $C_{22}H_{19}{}^{79}BrNO$ $[M+H]^+$: Calcd: 392.0650; Found: 392.0653;



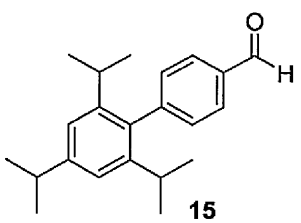
7s

(*4R,5S*)-4,5-Diphenyl-2-(2',4',6'-triisopropyl-3-methylbiphenyl-4-yl)-4,5-dihydrooxazole. The product (46 mg, 9% yield) was obtained as a white solid according to the general procedure;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.09 (d, $J$ = 6.9 Hz, 6H), 1.13 (d, $J$ = 6.9 Hz, 6H), 1.31 (d, $J$ = 6.9 Hz, 6H), 2.65 (septet, $J$ = 6.9 Hz, 2H), 2.78 (s, 3H), 2.95 (septet, $J$ = 6.9 Hz, 1H), 5.81 (d, $J$ = 10.2 Hz, 1H), 6.01 (d, $J$ = 10.2 Hz, 1H), 7.00-7.06 (m, 12H), 7.07-7.16 (m, 2H), 8.09 (d, $J$ = 7.8 Hz, 1H).



10

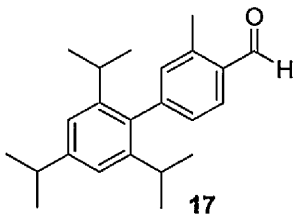
*N*-Benzyl-1-phenylethanamine.[46] The product (43 mg, 82% yield, 78% *ee*) was obtained according to the general hydrogenation procedure;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.29 (d, $J$ = 6.6 Hz, 3H), 3.51 (d, A of AB, $J_{AB}$ = 13.1 Hz, 1H), 3.58 (d, B of AB, $J_{AB}$ = 13.1 Hz, 1H), 3.73 (q, $J$ = 6.6 Hz, 1H), 7.13-7.27 (m, 10H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 23.4, 50.6, 56.4, 125.7, 125.8, 125.9, 127.1, 127.3, 127.4, 139.5, 144.4;
**HRMS** for $C_{15}H_{18}N$ $[M+H]^+$: Calcd: 212.1434; Found: 212.1429;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 99.9:0.1, flow rate 1 mL/min, λ = 220 nm): $t_R$ = 20.8 min (major), $t_R$ = 27.0 min (minor).



15

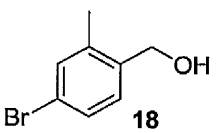
2',4',6'-Triisopropyl-[1,1'-biphenyl]-4-carbaldehyde.[42] The product (356 mg, 81% yield) was obtained as a white solid;
**IR** (neat): 1697 (s) $cm^{-1}$;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.01 (d, $J$ = 6.9 Hz, 12H), 1.24 (d, $J$ = 6.9 Hz, 6H), 2.43 (septet, $J$ = 6.9 Hz, 2H), 2.88 (septet, $J$ = 6.9 Hz, 1H), 7.00 (s, 2H), 7.29-7.31 (m, 2H), 7.84-7.87 (m, 2H), 10.01 (s, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 23.0, 23.1, 29.4, 33.3, 119.7, 128.4, 129.6, 133.9, 134.7, 145.0, 147.1, 147.6, 191.0;
**HRMS** for $C_{22}H_{29}O$ $[M+H]^+$: Calcd: 309.2213; Found: 309.2210;

**Anal Calcd** for $C_{22}H_{28}O$: C, 85.66; H, 9.15. Found: C, 85.74; H, 9.20.



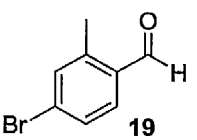

**17**

2',4',6'-Triisopropyl-3-methyl-[1,1'-biphenyl]-4-carbaldehyde. The product (78 mg, 24% yield) was obtained as a white solid;
**IR** (neat): 1697 (s) $cm^{-1}$;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.08 (d, $J$ = 6.6 Hz, 6H), 1.09 (d, $J$ = 6.7 Hz, 6H), 1.30 (d, $J$ = 6.8 Hz, 6H), 2.49-2.57 (m, 2H), 2.70 (s, 3H), 2.93 (septet, $J$ = 6.8 Hz, 1H), 7.05 (s, 2H), 7.10 (s, 1H), 7.20 (d, $J$ = 7.8 Hz, 1H), 7.84 (d, $J$ = 7.8 Hz, 1H), 10.31 (s, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 19.8, 24.0(8), 24.1(4), 24.3, 30.4, 34.2, 120.7, 128.0, 131.9, 132.7, 133.2, 135.8, 140.3, 146.0, 147.3, 148.5, 192.6;
**HRMS** for $C_{23}H_{30}O$ $[M+H]^+$: Calcd: 322.2297; Found: 322.2295;




**18**

(4-Bromo-2-methylphenyl)methanol.[47] The product (1.5 g, 49% yield) was obtained as a white solid;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 4.64 (s, 2H), 7.23 (d, $J$ = 8.6 Hz, 1H), 7.32-7.33 (m 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 18.9, 63.3, 121.8, 129.4(2), 129.4(4), 133.4, 138.0, 138.6;
**HRMS** for $C_8H_{11}BrN$ $[M+NH_4-H_2O]^+$: Calcd: 200.0069; Found: 200.0071.




**19**

4-Bromo-2-methylbenzaldehyde. The product (418 mg, 35% yield) was obtained as a white solid;
**IR** (neat): 1682 (s) $cm^{-1}$;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 2.65 (s, 3H), 7.45 (d, $J$ = 1.9 Hz, 1H), 7.51 (dd, $J$ = 8.2, 1.9 Hz, 1H), 7.66 (d, $J$ = 8.2 Hz, 1H), 10.22 (s, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 30.0, 127.2, 128.0, 133.2, 134.3, 143.5, 171.7, 201.5;
**HRMS** for $C_8H_8BrO$ $[M+H]^+$: Calcd: 198.9753; Found: 198.9748;
**Anal Calcd** for $C_8H_7BrO$: C, 48.27; H, 3.54. Found: C, 48.36; H, 4.34.

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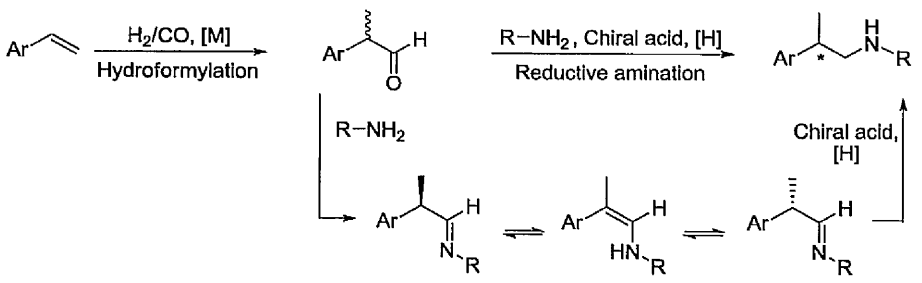
# Chapter 5

# Metal- and Organo-Catalysed Asymmetric Hydroaminomethylation

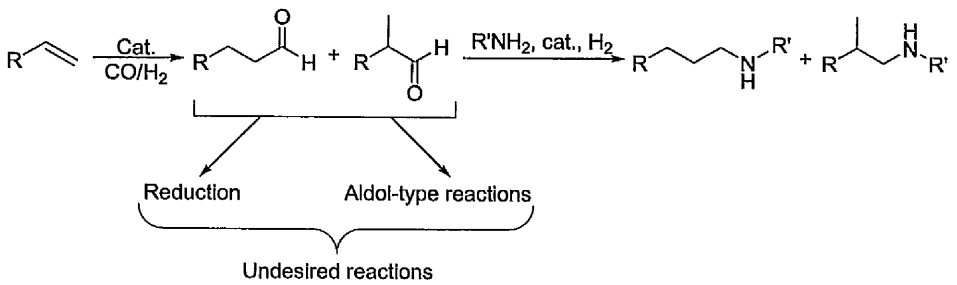
## 5.1 Introduction

Chapter 2 attempted the synthesis of β–chiral amines by DARA of α–branched aldehydes. As it was shown, only moderate enantioselectivities could be achieved with the cooperative chiral Ir-diamine/phosphate catalyst. This is not the only drawback on this reaction: α-branched aldehydes are not, in general, commercially available; therefore the synthesis of the starting aldehydes was required in order to develop a scope of substrates. This prompted us to design a more efficient pathway for the synthesis of β–chiral amines. We envisioned that a commercially available styrene could be selectively hydroformylated to the corresponding α–branched aldehyde, and following *in situ* condensation with an amine, asymmetric reduction of the enamine/imine would lead to the desired β–chiral amine (Scheme 5.1). The enantioselectivity would be obtained by dynamic kinetic resolution (DKR). In the presence of an acid catalyst, imines would undergo racemisation by fast tautomerisation. One of the enantiomers of the iminium cation could be selectively reduced leading to β–chiral amines (Scheme 5.1).[1]



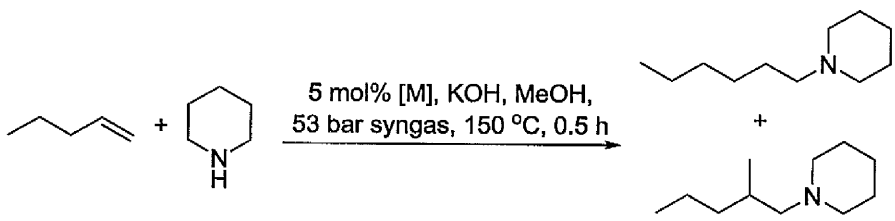

**Scheme 5.1**: Tandem hydroformylation/asymmetric reductive amination.

This sequential reaction, involving hydroformylation of an alkene, followed by reductive amination of the aldehyde intermediate with an amine, is also known as "hydroaminomethylation".[2] It represents a one-pot, atom-efficient reaction for the synthesis of amines. A suitable catalyst for hydroaminomethylation must fulfil a number of requirements (Scheme 5.2). It must be highly regioselective to either the linear or branched aldehyde, depending on the desired final product. The catalyst must be active for the enamine/imine hydrogenation, as a slow hydrogenation leads to aldol-type side reactions.[3] Finally, the catalyst must be selective for enamine/imine hydrogenation over hydrogenation of aldehydes. In addition, the enamine/imine isomerisation must be faster than the subsequent hydrogenation to ensure efficient DKR.




**Scheme 5.2**: Chemo- and regio-selectivity issues for the hydroaminomethylation sequence.

The first example of hydroaminomethylation was reported by Reppe at BASF in 1943.[4] Simple alkenes, like ethene or propene, were converted to secondary and tertiary amines in low yields, with ammonia under harsh conditions of 390 °C and 950 bar $H_2$ using $[Fe(CO)_5]$ in almost stoichiometric quantity. Iron catalysts resulted in low efficiency and were later substituted by the mixed-metal system ruthenium/iron,[5] rhodium catalysts[6] and cobalt catalysts.[7] For instance, Laine showed an enhancement in the activity with a mixed-metal catalyst.[5] A series of metal-carbonyl complexes were tested (Co, Os, Ir, Fe, Rh, Ru). In general, the most active hydroformylation catalysts were also the most active hydrogenation catalysts. There is a clear enhancement in the activity by using mixtures of ruthenium and iron, rather than the individual metals, which are relatively inefficient hydroaminomethylation catalysts (Scheme 5.3). IR spectra suggested that mixed-metal clusters formed in the reaction media.[5]



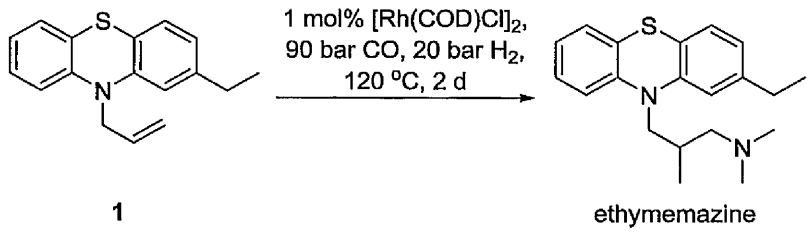

| Entry | [M] | TOF ($h^{-1}$) | *n/iso* selectivity |
|---|---|---|---|
| 1 | $Fe_3(CO)_{12}$ | 8 | 3:1 |
| 2 | $Ru_3(CO)_{12}$ | 20 | 49:1 |
| 3 | $Fe_3(CO)_{12}/Ru_3(CO)_{12}$ | 70 | 16:1 |

**Scheme 5.3**: Enhanced catalysis with combination of metal catalysts.

The group of Eilbracht has focused on the research of domino reactions involving hydroformylation as the first step.[8-15] Within this area, this group has

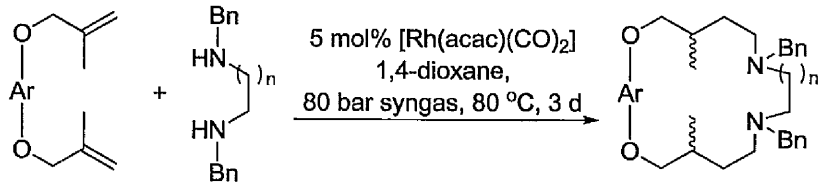
developed a wide range of syntheses based on the hydroaminomethylation sequence.[16-32] They have therefore reported the synthesis of a wide variety of compounds containing an amine functionality, including polyamines for azamacroheterocycles[22-23,31] and dendritic cores.[17,19,32]

Within the wide range of compounds with amine functionality synthesised *via* hydroaminomethylation by Eilbracht's group,[16-21,24,26-28,30] it is worth noting the synthesis of pharmacologically active $\gamma$- and $\delta$-aminofunctionalised phenothiazine, iminodibenzyl, carbazole and pyrazole derivatives. For instance, ethymemazine, an antihistaminicum, can be synthesised in one-pot from *N*-allylic amine **1** with 97% yield and 71% regioselectivity (Scheme 5.4).[28]



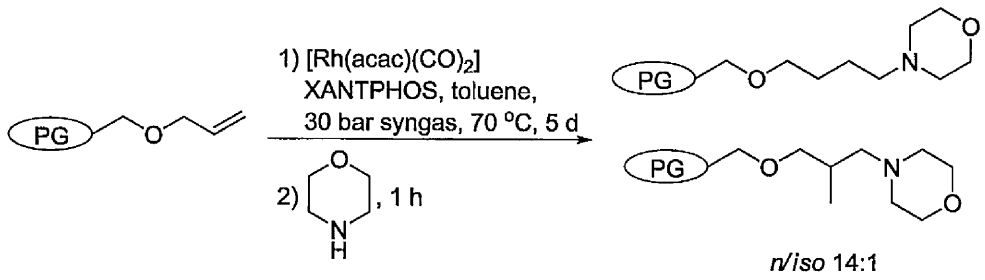

**Scheme 5.4**: Synthesis of antihitaminicum ethymemazine by hydroaminomethylation.

The hydroaminomethylation methodology was then extended to the synthesis of azamacroheterocyclic systems with up to 36 atoms, starting from easily available diolefins.[23] In a further publication, bismethylallyl systems were used to avoid mixtures of regioisomers (Scheme 5.5).[31] For these olefins, hydroformylation is expected to occur exclusively in the terminal position, leading to *n*-aldehydes.[31]




**Scheme 5.5**: Hydroaminomethylation of bismethylallyl systems.

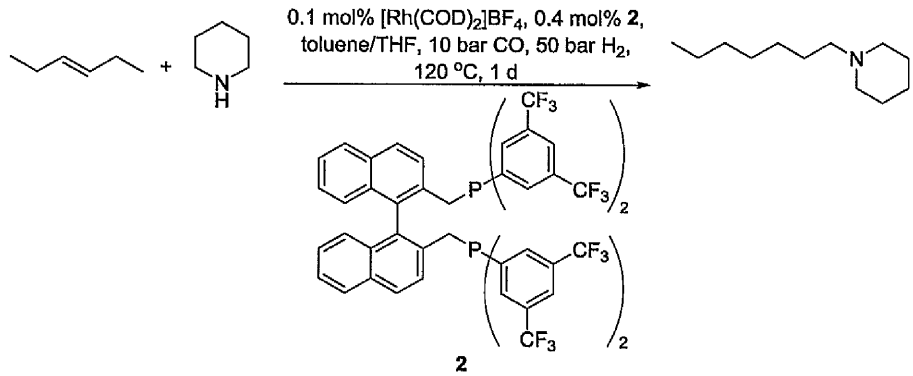
Initial investigations to generate amino-polyglycerols by hydroaminomethylation pathway were firstly reported using a Rh-XANTPHOS catalyst.[32] At the hydroformylation step, amines can coordinate to the catalyst and decrease the regioselectivity (*vide infra*). For this reason, the amine was added after quantitative conversion was observed for the hydroformylation step, leading to a one-pot but sequential procedure (Scheme 5.6). Further applications of this pathway to the synthesis of dendrimers were later described for the hydroaminomethylation of *N*-methylallylphthalimide[19] and for the convergent synthesis of polynitrile dendrimers.[16]




**Scheme 5.6:** Hydroaminomethylation of a polyallyl ether.

One of the most impressive examples of hydroaminomethylation was reported by Beller *et al.* in 2002.[33] Linear aliphatic amines were synthesised from internal olefins or olefin mixtures, where not only the

hydroaminomethylation pathway occurs in one-pot, but also the initial isomerisation of the alkene to the corresponding terminal alkene takes place, prior to the hydroformylation step. The reaction takes place with 0.1 mol% cationic Rh complex, 0.4 mol% ligand IPHOS **2**, in a toluene/tetrahydrofuran mixture (1:1) at 120 °C and 60 bar $CO/H_2$ (1:5) (Scheme 5.7). The active catalyst is capable of catalysing a fast isomerisation between the internal and terminal olefins and hydroformylation of the terminal alkene with high *n*-selectivity, and it is active and selective for the enamine hydrogenation.

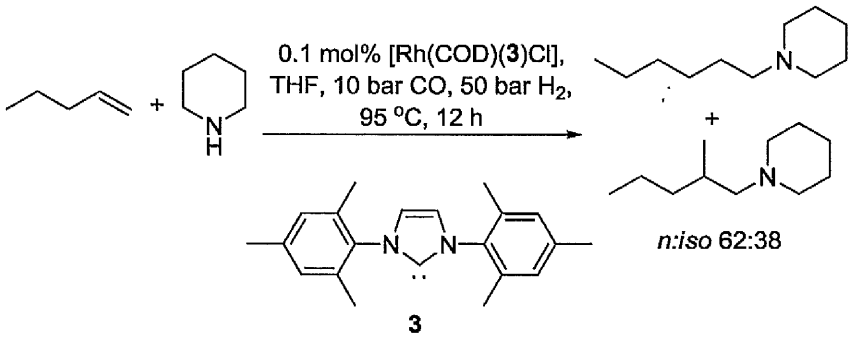



**2**

**Scheme 5.7**: Isomerisation of internal alkene followed by hydroaminomethylation.

Later in the decade, Beller's group reported the hydroaminomethylation of various aliphatic and aromatic olefins with a Rh-carbene catalyst.[34] Although the results did not surpass those from the previous publication, this is the only example where a Rh-carbene complex is used for this tandem reaction. The reaction takes place at 95 °C and 60 bar $CO/H_2$ (1:5) with 0.1 mol% catalyst loading in THF (Scheme 5.8). High linear selectivities are only obtained with α-substituted styrenes. However, the selectivity for aliphatic olefins is relatively low, in the range of 2-64% of the linear aldehyde, whilst

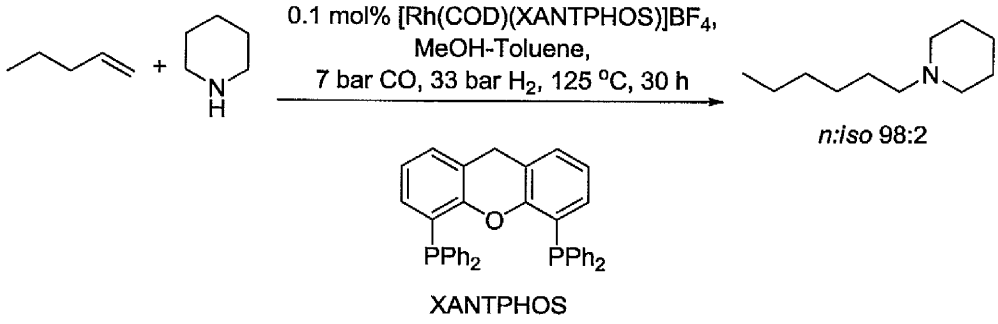
hydroformylation of styrene gives preferentially the branched aldehyde. The *n-iso* selectivity is determined at the hydroformylation step.




**Scheme 5.8:** Hydroaminomethylation with Rh-carbene catalyst.

The *n/iso* selectivity is, therefore, one of the main drawbacks for this domino reaction. The same group then decided to focus their studies on the regioselectivity of different catalysts applied to hydroaminomethylation. Although the regioselectivity of hydroformylation catalysts has been widely studied, the presence of the amine influences the regioselectivity, as it may compete with the ligand for the metal centre. Indeed, the presence of triethylamine decreases the *n/iso* selectivity from 95:5 to 80:20, for the hydroformylation of 1-pentene with a Rh-$PPh_3$ catalyst.[3] As expected, chelating phosphines maintain high selectivity as they make ligand exchange less favourable, XANTPHOS being the most regioselective ligand with 97:3 *n/iso* selectivity in the presence of triethylamine. The cationic Rh-XANTPHOS catalyst is effective for a large number of aliphatic and aromatic olefins bearing a wider variety of functional groups, as well as primary and secondary amines possessing functional groups.[3] High regioselectivities (90:10 to 99:1 *n/iso* selectivity) are obtained in general. Even when styrene is used, the *n/iso*

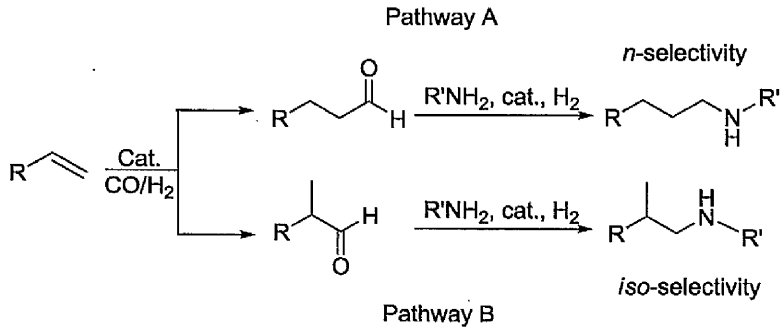
selectivity is 82:18; this value is very high taking into account that hydroformylation of styrene gives preferentially the branched product in general.[35] An example is shown in Scheme 5.9, where the reaction takes place in MeOH-toluene, under 40 bar $CO/H_2$ (4.7:1) and 125 °C with 0.1 mol% catalyst loading.




**Scheme 5.9:** Hydroaminomethylation with cationic Rh-XANTPHOS catalyst.

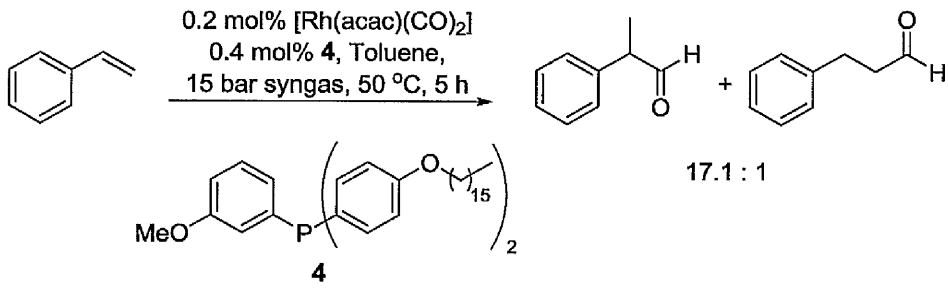
## 5.2 Results and Discussion

As shown in Section 5.1., hydroaminomethylation has been widely reported in the literature as an effective pathway for the synthesis of achiral amines. In this regard, the linear aldehyde is usually the desired product in the hydroformylation step. This leads to the formation of a single amine (Scheme 5.10, pathway A). On the other hand, the branched aldehyde leads to a racemic mixture of two enantiomeric amines (Scheme 5.10, pathway B). Due to the selectivity issue, until now, hydroaminomethylation has been most useful for the synthesis of amines derived from linear aldehydes.



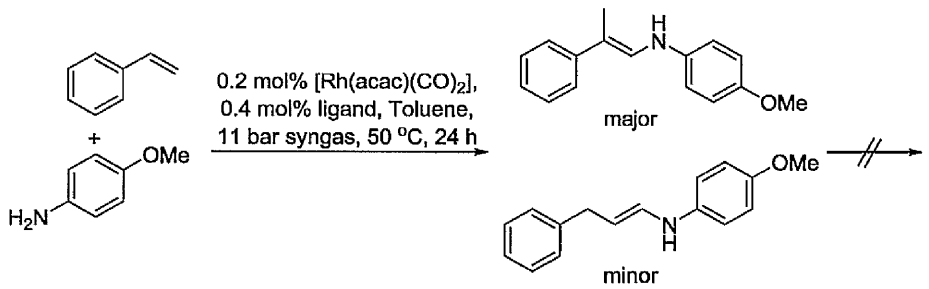

**Scheme 5.10**: *n/iso* Regioselectivities for the hydroaminomethylation sequence.

However, the main aim of this chapter is the synthesis of β–chiral amines. Therefore, a catalyst that offers high selectivity for the branched aldehyde is required, where a stereogenic centre is formed. Li and co-workers reported the selective hydroformylation of styrene to the corresponding α–branched aldehyde with a rhodium catalyst containing a triarylphosphine ligand possessing a long-chain alkoxy group.[36] The reaction takes place in toluene, with 0.2 mol% [Rh(acac)(CO)$_2$], 0.4 mol% phosphine ligand, at 15 bar syngas and 50 °C (Scheme 5.11). As a starting point, we decided to use these conditions for the hydroaminomethylation sequence.



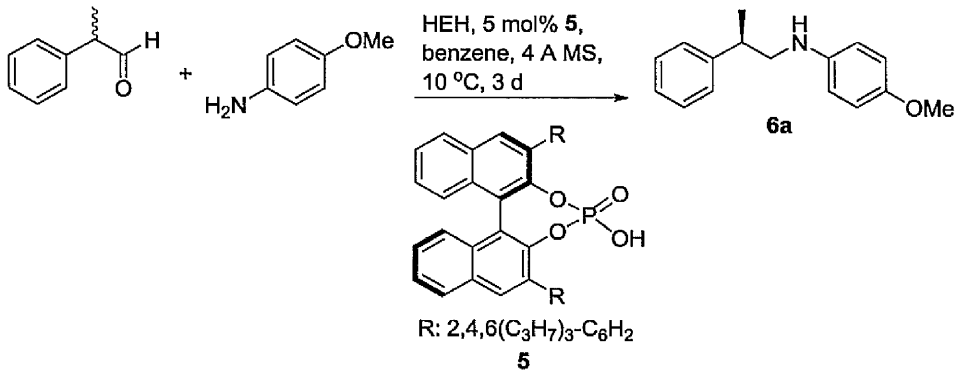

**Scheme 5.11**: Hydroformylation of styrene with Rh-**4**.

Preliminary studies with different phosphine ligands, e.g. $PPh_3$, (*R*)-BINAP, (*S*)-PHAPHOS, (*R,R*)-BDPP, among others, showed different *n/iso* selectivities for the hydroformylation of styrene, as well as enamine formation (Scheme 5.12). Hydrogenation of the enamine was never observed, showing that these Rh-phosphine hydroformylation catalysts are ineffective for the hydrogenation step. This is not surprising as one of the main problems for the current hydroaminomethylation protocols is the slow hydrogenation of the enamine/imine intermediate.[3]



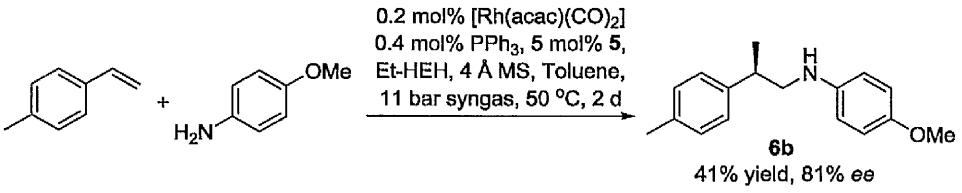

**Scheme 5.12**: Preliminary studies on the hydroaminomethylation of styrene.

We then turned our attention to the use of two different catalysts for the hydroformylation and hydrogenation steps. As mentioned in Chapter 2, List *et al.* developed the DARA of α–branched aldehydes via DKR using a chiral phosphoric acid as organocatalyst and HEH as the hydrogen source (Scheme 5.13).[37] This became our catalyst of choice for the reductive amination step.




**Scheme 5.13:** DARA of an α–branched aldehyde with chiral organocatalyst.

We combined the $[Rh(acac)(CO)_2]$ catalyst precursor with $PPh_3$, Et-HEH and **5** in toluene at 11 bar syngas and 50 °C for the reaction of *p*-methylstyrene and *p*-anisidine. The reaction was left stirring for 2 days. Gratifyingly, after flash chromatography purification, a very promising 41% isolated yield was obtained for the desired product **6b** with a good enantioselectivity of 81% *ee* (Scheme 5.14).

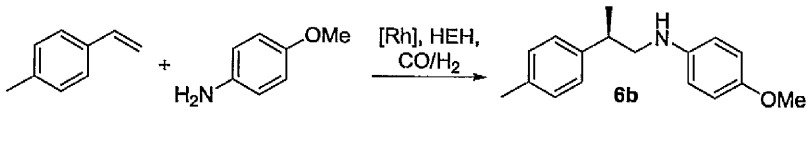


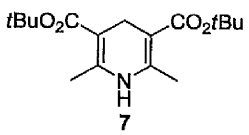

**Scheme 5.14**: Preliminary study on the metal- and organo-catalysed asymmetric hydroaminomethylation.

Encouraged by this result, optimisation of conditions was then undertaken for an improvement in the yield. First, the effect of the HEH was studied. The results are listed in Table 5.1. The reaction takes place under syngas pressure;

therefore $H_2$ could act as the reductant for the hydrogenation step. However, the experiments show that the presence of HEH is essential in this reaction (entry 1). An excess of Et-HEH provides a positive effect on the yield (entry 2 vs entry 3). A bulkier *t*Bu-HEH **7** provided an increase in the enantioselectivity for the DARA of α-branched aldehydes.[37] We therefore studied the effect of **7** on this procedure. Unfortunately, very low yield was obtained (entry 5). A decrease in the activity with bulkier HEH's was also observed by List *et al.*[37]

**Table 5.1**: Effect of Hantzsch ester on the asymmetric hydroaminomethylation of *p*-methylstyrene with *p*-anisidine.[a]



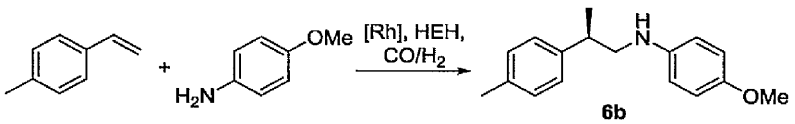

| Entry | Eqs. Et-HEH | Yield (%)[b] | *Ee* (%)[c] |
|---|---|---|---|
| 1 | - | N.R.[d] | N.D.[e] |
| 2 | 1.2 | 40 | 81 |
| 3 | 2.2 | 67 | 80 |
| 4 | 4.0 | 64 | 80 |
| 5 | 1.2 eq **7** | < 10 | N.D.[e] |

[a]Reaction conditions: 0.4 mmol *p*-methylstyrene, 0.25 mmol *p*-anisidine, 1.25 μmmol [Rh(acac)$(CO)_2$], 2.5 μmmol $PPh_3$, Et-HEH (unless otherwise specified), 12.5 μmmol **5**, 100 mg 4 Å MS, 4 mL toluene, 11 bar $CO/H_2$ 1:1, 50 °C, 2 d. [b]Isolated yield. [c]Determined by HPLC. [d]N.R., no reaction. [e]N.D., not determined.

The effect of the temperature was also studied. The optimal temperature for the hydroformylation step is 50 °C,[36] while better enantioselectivities are

obtained a low temperature of 6 °C for the reductive amination step in the organocatalysis.[37] There was indeed an increase in enantioselectivity when the temperature was dropped to 25 °C; however, the hydroformylation did not reach completion after 3 days (Table 5.2, entry 2). A higher temperature of 80 °C led to higher yield but a slight decrease in enantioselectivity (entry 3). A temperature of 50 °C was finally chosen that offered good enantioselectivities whilst still maintaining a reasonable rate of reaction.

**Table 5.2:** Effect of temperature on the asymmetric hydroaminomethylation of *p*-methylstyrene with *p*-anisidine.[a]




**6b**

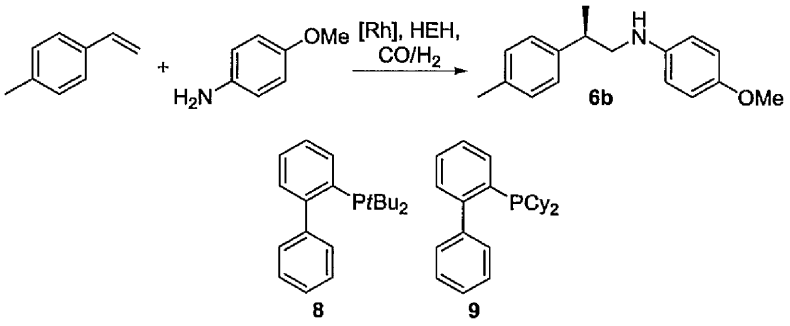
| Entry | Temp. (°C) | Time (d) | Yield (%)[b] | *Ee* (%)[c] |
|---|---|---|---|---|
| 1 | 50 | 2 | 40 | 81 |
| 2 | 25 | 3 | 24 | 83 |
| 3 | 80 | 2 | 55 | 79 |

[a]Reaction conditions were the same as those in Table 5.1 except with 0.6 mmol Et-HEH, temperature and time. [b]Isolated yield. [c]Determined by HPLC.

Table 5.3 shows the effect of the phosphines ligand in this asymmetric hydroaminomethylation procedure. Monophosphine ligands are in general superior compared to diphosphine ligands (entries 1-3 *vs* 4-8). Within derivatives of $PPh_3$, a more electron-donating substituent in the ligand leads to an increase in yield (entry 8), while an electron-deficient substituent has a negative effect on the yield (entry 7). We can rationalise that the increase in yield results from a higher selectivity for the branched aldehyde in the

hydroformylation step. Moser and co-workers showed that *p*-electron-donating groups in the phosphine increase the basicity of the phosphine and the selectivity for α-branched aldehydes.[38]

**Table 5.3:** Effect of the ligand on the asymmetric hydroaminomethylation of *p*-methylstyrene with *p*-anisidine.[a]



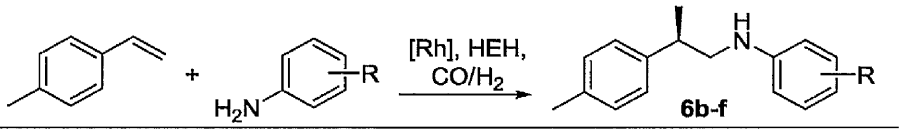

| Entry | Ligand | Yield (%)[b] |
|---|---|---|
| 1 | DPPP | N.R.[c] |
| 2 | DPPB | N.R.[c] |
| 3 | XANTPHOS | 20 |
| 4 | **8** | <5 |
| 5 | **9** | 43 |
| 6 | $PPh_3$ | 30 |
| 7 | $(4\text{-}CF_3C_6H_4)_3P$ | 25 |
| 8 | $(4\text{-}MeOC_6H_4)_3P$ | 48 |

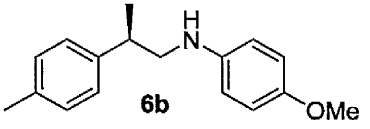
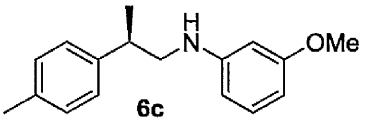
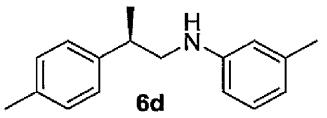
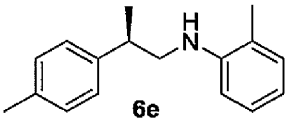
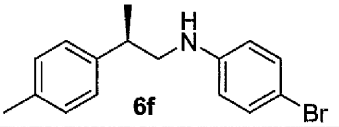
[a]Reactions conditions were the same as those in Table 5.1 except with different phosphine ligand, 0.6 mmol Et-HEH and 17 hours reaction time. [b]Isolated yield. [c]N.R., no reaction, only linear product obtained.

The generality of the methodology is shown in Tables 5.4 and 5.5, using a range of styrenes and anilines under the optimised conditions. Table 5.4 shows the effect of substituents at the aniline on the hydroaminomethylation of *p*-methylstyrene. All the products **6b-f** were obtained with good

enantioselectivity (78-86% *ee*). Better enantioselectivities were obtained when more sterically-hindered anilines were used (entry 1 *vs* 2, entry 3 *vs* 4). This observation was previously shown in the DARA of ketones.[39-40] Lower yield was obtained when using electron-deficient *p*-bromoaniline (entry 5). This was also observed by List in the organocatalytic DARA of α–branched aldehydes by DKR[37] and in transition metal-[41] and organo-catalysed[42-43] DARA of ketones, previously described in Chapter 2.

**Table 5.4**: Asymmetric hydroaminomethylation of *p*-methylstyrene with different anilines.[a]

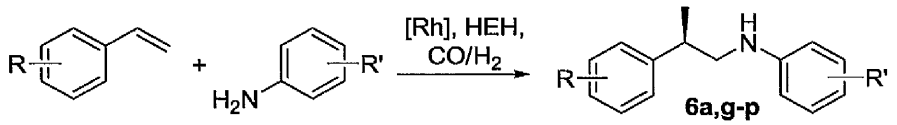


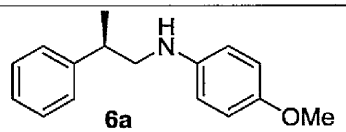
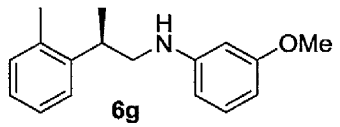
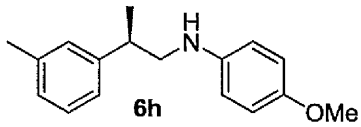
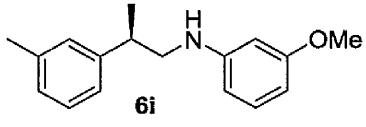
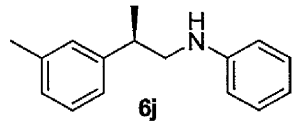

| Entry | R | Product | Yield (%)[b] | *Ee* (%)[c] |
|---|---|---|---|---|
| 1 | *p*-OMe |  | 79 | 80 |
| 2 | *m*-OMe |  | 83 | 84 |
| 3 | *m*-Me |  | 87 | 78 |
| 4 | *o*-Me |  | 61 | 86 |
| 5 | *p*-Br |  | 45 | 79 |

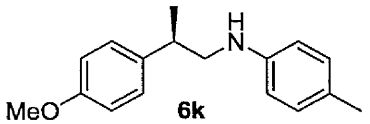
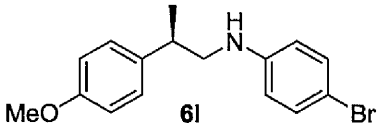
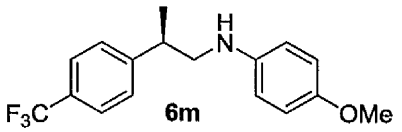
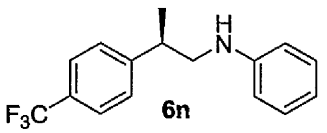
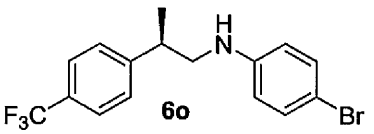
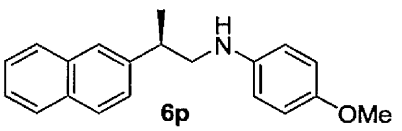
[a]Reactions conditions were the same as those in Table 5.1 except with 0.25 mmol aniline derivative, 2.5 μmmol $(4\text{-}CH_3OC_6H_4)_3P$, 0.6 mmol Et-HEH and 3 d reaction time. [b]Isolated yield. [c]Determined by HPLC.

We next investigated the asymmetric hydroaminomethylation of different derivatives of styrene with aniline and its analogues (Table 5.5). Good yields and enantioselectivities were obtained in general. A lower yield was obtained when using an *ortho*-substituted styrene (entry 4). This is due to the branched/linear (b:l) selectivity in the hydroformylation step being lower as a result of steric effects, with the *ortho* substituent inhibiting the formation of the benzylic Rh-species that would favour producing the branched aldehyde.[44-45] In fact, when hydroformylation of *p*-methyl and *o*-methylstyrene was compared, the *n/iso* selectivity decreased from 1:13.3 to 1:6.7.

**Table 5.5:** Asymmetric hydroaminomethylation of different derivatives of styrene.[a]




| Entry | R | R' | Product | Yield (%)[b] | *Ee* (%)[c] |
|---|---|---|---|---|---|
| 1 | H | *p*-OMe |  **6a** | 80 | 83 |
| 2 | *o*-Me | *m*-OMe |  **6g** | 49 | 91 |
| 3 | *m*-Me | *p*-OMe |  **6h** | 61 | 80 |
| 4 | *m*-Me | *m*-OMe |  **6i** | 78 | 84 |
| 5 | *m*-Me | H |  **6j** | 56 | 80 |

| | | | | | |
|---|---|---|---|---|---|
| 6 | *p*-OMe | *p*-Me |  **6k** | 61 | 82 |
| 7 | *p*-OMe | *p*-Br |  **6l** | 51 | 84 |
| 8 | *p*-$CF_3$ | *p*-OMe |  **6m** | 70 | 81 |
| 9 | *p*-$CF_3$ | H |  **6n** | 56 | 79 |
| 10 | *p*-$CF_3$ | *p*-Br |  **6o** | <5 | N.D.[d] |
| 11 | R[e] | *p*-OMe |  **6p** | 81 | 83 |

[a]Reactions conditions were the same as those in Table 5.1 except with 0.4 mmol styrene derivative, 0.25 mmol aniline derivative, 2.5 μmmol $(4\text{-}CH_3OC_6H_4)_3P$, 0.6 mmol Et-HEH and 3 d reaction time. [b]Isolated yield. [c]Determined by HPLC. [d]N.D., not determined. [e]2-vinylnaphthalene (R: 3,4-$C_4H_4$) used as olefin.

Similar to what is shown in Table 5.4, electron-deficient groups in the aniline ring have a negative effect on the yield (Table 5.5, entries 3, 6, 9-10). This is likely to result from an inefficient condensation reaction of the aniline with the aldehyde.[37,43] The same could be expected from electron-deficient groups in the styrene ring (entries 8-10).[37] However, higher selectivities for the branched aldehyde in the hydroformylation step are expected with electron-withdrawing groups in the styrene.[46] This could explain the good yield obtained for product **6n** (entry 8).

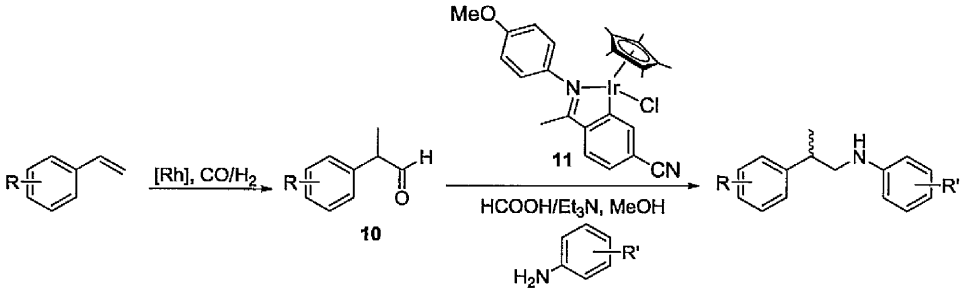
## 5.3 Conclusions and Future work

The synthesis of β-chiral amines has been achieved with good yields and enantioselectivities following a tandem hydroformylation/reductive amination procedure. To our knowledge, this is the first example of an asymmetric version of this sequential procedure. This first asymmetric hydroaminomethylation is made feasible by combining metal- and organo-catalysis in a tandem fashion. This provides an attractive pathway for the synthesis of β-chiral amines, as they can be obtained in one step from commercially available starting materials.

The main drawbacks of organocatalytic reduction with HEH as hydrogen source are the long reaction times required, as well as the production of stoichiometric amounts of pyridine by-product. A single chiral organometallic complex to catalyse the three steps will be more desirable. This would lead to a greener procedure where $H_2$ would be the only hydrogen source.

## 5. 4 Experimental

### General procedure for the synthesis of racemic mixtures of 6a-p




To a glass liner equipped with a stir bar was added alkene (5 mmol), $[Rh(acac)(CO)_2]$ (25 μmol), $(4\text{-}MeOC_6H_4)_3P$ (50 μmol) and toluene (2 mL).

The glass liner was then placed into an autoclave, followed by degassing with syngas three times. The reaction was carried out at 11 bar syngas with stirring at 50 °C overnight. The stirring was then stopped, and the autoclave allowed to cool down to room temperature. The syngas was then carefully released in a fume hood and the solution was filtered through celite, transferred to a flask, and concentrated to afford the crude product. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (50/1) yielded the desired aldehyde product **10**.

To an oven-dried Schlenk tube equipped with a stir bar was added **10** (0.5 mmol), amine (0.5 mmol) and **11** (5 μmol).[47] The tube was degassed with nitrogen three times. MeOH (4 mL) was then added with syringe, followed by HCOOH/$Et_3N$ (5:2, 1 mL). The resulting mixture was stirred at 80 °C for 3 hours. The stirring was then stopped, and the reaction mixture allowed to cool down to room temperature. The reaction was then quenched with water and basified with saturated $KOH_{(aq)}$ solution, extracted with ethyl acetate and dried over $MgSO_4$. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (15/1) yielded the racemic mixtures of **6a-p**.

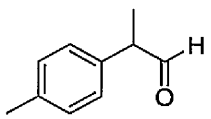
**General procedure for asymmetric hydroaminomethylation**

To a glass liner equipped with a stir bar was added 4 Å MS (100 mg), alkene (0.4 mmol), amine (0.25 mmol), [Rh(acac)$(CO)_2$] (1.25 μmol), (4-MeO-$C_6H_4)_3P$ (2.5 μmol), Et-HEH (0.6 mmol), **5** (12.5 μmol) and toluene (2 mL). The glass liner was then placed into an autoclave, followed by degassing with

syngas three times. The reaction was carried out at 11 bar syngas with stirring at 50 °C for 3 d. The stirring was then stopped, and the autoclave allowed to cool down to room temperature. The syngas was then carefully released in a fume hood and the solution was filtered through celite, transferred to a flask, and concentrated to afford the crude product. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (40/1 to 30/1) yielded the desired amine product.

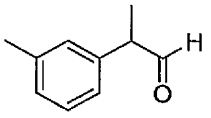
## 5.5 Analytical data

Aldehydes **10a-f** were synthesised as intermediates for the preparation of racemic mixtures of amines **6a-p**. They are known compounds; therefore, only $^{1}H$ and $^{13}C$ NMR spectra have been acquired. Compounds **6c-n** are new compounds.



**10a**

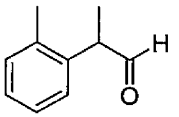
2-*p*-Tolylpropanal.[37] The product (0.46 g, 62% yield) was obtained as a colourless oil according to the general procedure in 5 h;
**$^{1}H$ NMR** (400 MHz, $CDCl_3$) δ 1.33 (d, $J$ = 7.0 Hz, 3H), 2.26 (s, 3H), 3.51 (qd, $J$ = 7.0, 1.4 Hz, 1H), 7.01 (d, $J$ = 8.0 Hz, 2H), 7.10 (d, $J$ = 8.0 Hz, 2H), 9.57 (d, $J$ = 1.4 Hz, 1H);
**$^{13}C$ NMR** (100 MHz, $CDCl_3$) δ 14.6, 21.1, 52.7, 128.2, 129.8, 134.6, 137.3, 201.4.



**10b**

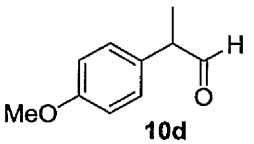
2-*m*-Tolylpropanal.[48] The product (0.50 g, 67% yield) was obtained as a colourless oil according to the general procedure in 5 h;
**$^{1}H$ NMR** (400 MHz, $CDCl_3$) δ 1.43 (d, $J$ = 7.0 Hz, 3H), 2.36 (s, 3H), 3.59 (qd, $J$ = 7.0, 1.3 Hz, 1H), 7.00-7.02 (m, 2H), 7.12 (dd, $J$ = 7.8, 0.5 Hz, 1H), 7.27 (t, $J$ = 7.8 Hz, 1H), 9.67 (d, $J$ = 1.3 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 15.0, 21.8, 53.4, 125.8, 128.7, 129.4, 129.5, 138.0, 139.2, 201.6.



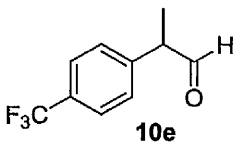
**10c**

2-*o*-Tolylpropanal.[49] The product (0.33 g, 45% yield) was obtained as a colourless oil according to the general procedure in 5 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.65 (d, $J$ = 7.0 Hz, 3H), 2.37 (s, 3H), 3.85 (q, $J$ = 7.0 Hz, 1H), 7.05-7.09 (m, 1H), 7.18-7.26 (m, 3H), 9.66 (d, $J$ = 1.1 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 14.3, 19.6, 49.3, 126.0, 127.4, 127.5, 130.9, 136.3, 136.6, 201.0.



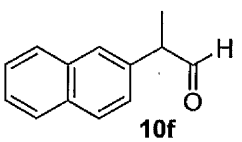
**10d**

2-(4-Methoxyphenyl)propanal.[50] The product (0.53 g, 64% yield) was obtained as a colourless oil according to the general procedure in 5 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.41 (d, $J$ = 7.1 Hz, 3H), 3.58 (qd, $J$ = 7.1, 1.5 Hz, 1H), 3.80 (s, 3H), 6.89-6.93 (m, 2H), 7.11-7.14 (m, 2H), 9.64 (d, $J$ = 1.5 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 14.6, 52.1, 55.3, 114.5, 129.3, 129.5, 159.0, 201.2;



**10e**

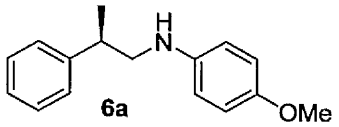
2-(4-(Trifluoromethyl)phenyl)propanal.[50-51] The product (0.73 g, 72% yield) was obtained as a colourless oil according to the general procedure from in 5 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.49 (d, $J$ = 7.1 Hz, 3H), 3.73 (qd, $J$ = 7.1, 1.2 Hz, 1H), 7.34 (d, $J$ = 8.1 Hz, 2H), 7.65 (d, $J$ = 8.1 Hz, 2H), 9.70 (d, $J$ = 1.2 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 15.0, 53.1, 126.4 (q, $J_{CF}$ = 3.7 Hz), 127.1 (q, $J_{CF}$ = 270.6 Hz), 129.1, 130.3 (q, $J_{CF}$ = 31.7 Hz), 142.2, 200.5;



**10f**

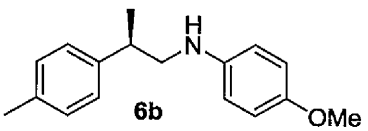
2-(Naphthalen-2-yl)propanal.[37] The product (0.52 g, 56% yield) was obtained as a white solid according to the general procedure in 17 h;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.54 (d, $J$ = 7.0 Hz, 3H), 3.82 (qd, $J$ = 7.0, 1.2 Hz, 1H), 7.32 (dd, $J$ = 8.4, 1.8 Hz, 1H), 7.46-7.53 (m, 2H), 7.68 (d, $J$ = 0.7 Hz, 1H), 7.82-7.88 (m, 3H), 9.77 (d, $J$ = 1.2 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 15.1, 53.5, 117.7, 126.5, 126.6, 126.9, 127.6, 128.1, 129.3, 133.1, 134.0, 135.5, 201.5;



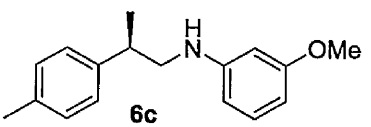
**6a**

4-Methoxy-*N*-(2-phenylpropyl)aniline.[37] The product (45 mg, 74% yield, 83% *ee*) was obtained as a colourless oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.32 (d, $J$ = 7.0 Hz, 3H), 3.00-3.08 (m, 1H), 3.19 (dd, A of ABX, $J_{AB}$ = 12.2 Hz, $J_{AX}$ = 8.3 Hz, 1H), 3.30 (dd, B of ABX, $J_{AB}$ = 12.2 Hz, $J_{BX}$ = 6.1 Hz, 1H), 3.74 (s, 3H), 6.52-6.56 (m, 2H), 6.74-6.77 (m, 2H), 7.21-7.25 (m, 3H), 7.30-7.35 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 19.8, 39.2, 52.0, 55.8, 114.4, 114.9, 126.6, 127.3, 128.7, 142.4, 144.6, 152.1;
**HRMS** for $C_{16}H_{20}NO$ $[M+H]^+$: Calcd: 242.1539; Found: 242.1537;
**HPLC** (Chiralcel OJ, hexane:isopropanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 19.6 min (minor), $t_R$ = 23.1 min (major).



**6b**

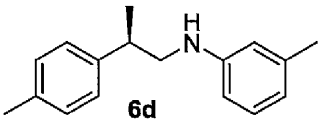
4-Methoxy-*N*-(2-*p*-tolylpropyl)aniline.[37] The product (50 mg, 79% yield, 80% *ee*) was obtained as a colourless oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.30 (d, $J$ = 7.0 Hz, 3H), 2.33 (s, 3H), 2.98-3.05 (m, 1H), 3.16 (dd, A of ABX, $J_{AB}$ = 12.1 Hz, $J_{AX}$ = 8.4 Hz, 1H), 3.28 (dd, B of ABX, $J_{AB}$ = 12.1 Hz, $J_{BX}$ = 6.2 Hz, 1H), 3.74 (s, 3H), 6.53-6.57 (m, 2H), 6.74-6.78 (m, 2H), 7.10-7.15 (m, 4H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 20.0, 21.1, 38.8, 52.1, 55.8, 114.4, 114.9, 127.2, 129.4, 136.1, 141.6, 142.4, 152.1;
**HRMS** for $C_{17}H_{22}NO$ $[M+H]^+$: Calcd: 256.1701; Found: 256.1706;
**HPLC** (Chiralcel OJ, hexane:isopropanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 16.5 min (minor), $t_R$ = 18.7 min (major).



**6c**

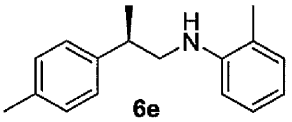
3-Methoxy-*N*-(2-*p*-tolylpropyl)aniline. The product (53 mg, 83% yield, 84% *ee*) was obtained as a colourless oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.31 (d, $J$ = 6.9 Hz, 3H), 2.33 (s, 3H), 2.97-3.06 (m, 1H), 3.19 (dd, A of ABX, $J_{AB}$ = 12.2 Hz, $J_{AX}$ = 8.3 Hz, 1H), 3.30 (dd, B of ABX, $J_{AB}$ = 12.2 Hz, $J_{BX}$ = 6.2 Hz, 1H), 3.75 (s, 3H), 6.13 (t, $J$ = 2.1 Hz, 1H), 6.18 (dd, $J$ = 8.1, 2.1 Hz, 1H), 6.25 (dd, $J$ = 8.1, 2.1 Hz, 1H), 7.05 (t, $J$ = 8.1 Hz, 1H), 7.10-7.15 (m, 4H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 18.5, 21.0, 38.8, 50.9, 55.1, 98.8, 102.4, 106.1, 127.1, 129.3, 129.9, 136.1, 141.4, 149.5, 160.8;
**HRMS** for $C_{17}H_{22}NO$ $[M+H]^+$: m/z Calcd: 256.1696; Found: 256.1698;

**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 30.1 min (minor), $t_R$ = 37.2 min (major).



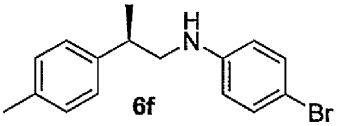
**6d**

3-Methyl-*N*-(2-*p*-tolylpropyl)aniline. The product (52 mg, 87% yield, 78% *ee*) was obtained as a clear yellow oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.31 (d, $J$ = 7.0 Hz, 3H), 2.26 (s, 3H), 2.34 (s, 3H), 2.97-3.05 (m, 1H), 3.19 (dd, A of ABX, $J_{AB}$ = 12.2 Hz, $J_{AX}$ = 8.3 Hz, 1H), 3.31 (dd, B of ABX, $J_{AB}$ = 12.2 Hz, $J_{BX}$ = 6.2 Hz, 1H), 3.52 (brs, 1H), 6.38-6.39 (m, 2H), 6.51 (d, $J$ = 7.4 Hz, 1H), 7.02-7.06 (m, 1H), 7.11-7.15 (m, 4H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 20.0, 21.2, 21.8, 39.0, 51.1, 110.2, 113.9, 118.4, 127.3, 129.2, 129.5, 136.2, 139.0, 141.7, 148.4;
**HRMS** $C_{17}H_{22}N$ $[M+H]^+$: Calcd: 240.1747; Found: 240.1744;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 99.8:0.2, flow rate 1 mL/min, λ = 254 nm): $t_R$ = 20.2 min (minor), $t_R$ = 20.9 min (major).



**6e**

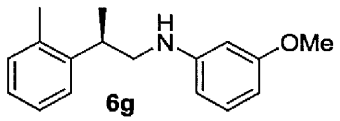
2-Methyl-*N*-(2-*p*-tolylpropyl)aniline. The product (36 mg, 61% yield, 86% *ee*) was obtained as a colourless oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.34 (d, $J$ = 6.9 Hz, 3H), 1.93 (s, 3H), 2.33 (s, 3H), 3.04-3.09 (m, 1H), 3.19 (dd, A of ABX, $J_{AB}$ = 11.9 Hz, $J_{AX}$ = 8.4 Hz, 1H), 3.37 (dd, B of ABX, $J_{AB}$ = 12.0 Hz, $J_{BX}$ = 5.8 Hz, 1H), 3.43 (brs, 1H), 6.64 (d, $J$ = 7.7 Hz, 2H), 7.00, (d, $J$ = 7.4 Hz, 1H), 7.10-7.12 (m, 5H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 17.2, 19.6, 21.0, 38.7, 51.0, 109.9, 116.8, 122.1, 127.1, 129.4, 129.5, 130.0, 136.2, 141.4, 146.1;
**HRMS** for $C_{17}H_{22}N$ $[M+H]^+$: Calcd: 240.1747; Found: 240.1746;
**HPLC** (Chiralcel OD-H, hexane :isopropanol = 99:1, flow rate 1 mL/min, λ = 254 nm): $t_R$ = 7.2 min (major), $t_R$ = 7.9 min (minor).



**6f**

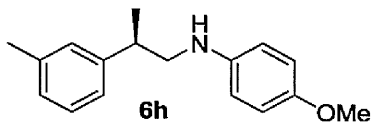
4-Bromo-*N*-(2-*p*-tolylpropyl)aniline. The product (34 mg, 45% yield, 79% *ee*) was obtained as a clear oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.30 (d, $J$ = 7.0 Hz, 3H), 2.33 (s, 3H), 2.95-3.03 (m, 1H), 3.15 (dd, A of ABX, $J_{AB}$ = 12.3 Hz, $J_{AX}$ = 8.5 Hz, 1H), 3.28 (dd, B of ABX, $J_{AB}$ = 12.3 Hz, $J_{BX}$ = 6.0 Hz, 1H), 3.57 (brs, 1H), 6.41-6.44 (m, 2H), 7.08-7.14 (m, 4H), 7.19-7.23 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 19.8, 21.0, 38.7, 50.9, 108.8, 114.5, 127.5, 129.4, 131.9, 136.3, 141.1, 147.1;
**HRMS** for $C_{16}H_{19}{}^{79}BrN$ $[M+H]^+$: Calcd: 304.0701; Found: 304.0704;

**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 14.7 min (minor), $t_R$ = 15.3 min (major).



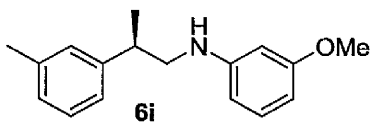

**6g**

3-Methoxy-*N*-(2-(*o*-tolyl)propyl)aniline. The product (31 mg, 49% yield, 91% *ee*) was obtained a pale yellow oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.4 Hz, 3H), 2.24 (s, 3H), 3.18-3.32 (m, 3H), 3.54 (brs, 1H), 3.68 (s, 3H), 6.06 (t, *J* = 2.2 Hz, 1H), 6.11 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.18 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.98 (t, *J* = 8.0 Hz, 1H), 7.04-7.11 (m, 2H), 7.13-7.15 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 19.6 (2C), 34.2, 50.2, 55.1, 98.8, 102.5, 106.0, 125.3, 126.2, 126.5, 129.9, 130.5, 136.2, 142.6, 149.6, 160.9;
**HRMS** for $C_{17}H_{22}NO$ $[M+H]^+$: Calcd: 256.1701; Found: 256.1703;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 41.3 min (minor), $t_R$ = 52.7 min (major).




**6h**

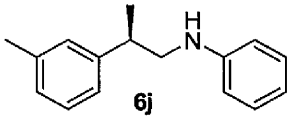
4-Methoxy-*N*-(2-*m*-tolylpropyl)aniline. The product (39 mg, 61% yield, 80% *ee*) was obtained as a pale yellow oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.31 (d, *J* = 7.0 Hz, 3H), 2.35 (s, 3H), 2.97-3.03 (m, 1H), 3.18 (dd, A of ABX, $J_{AB}$ = 12.1 Hz, $J_{AX}$ = 8.3 Hz, 1H), 3.28 (dd, B of ABX, $J_{AB}$ = 12.1 Hz, $J_{BX}$ = 6.1 Hz, 1H), 3.74 (s, 3H), 6.53-6.57 (m, 2H), 6.74-6.78 (m, 2H), 7.01-7.06 (m, 3H), 7.21 (d, *J* = 8.2 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 20.0, 21.6, 39.3, 52.1, 55.9, 114.5, 115.0, 124.4, 127.5, 128.1, 128.7, 138.4, 142.5, 144.7, 152.2;
**HRMS** for $C_{17}H_{22}NO$ $[M+H]^+$: Calcd: 256.1701; Found: 256.1700;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 99:1, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 42.7 min (major), $t_R$ = 49.9 min (minor).




**6i**

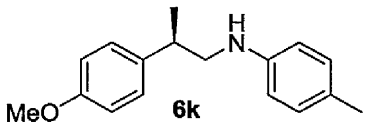
3-Methoxy-*N*-(2-(*m*-tolyl)propyl)aniline. The product (50 mg, 78% yield, 84% *ee*) was obtained as a pale yellow oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.24 (d, *J* = 7.0 Hz, 3H), 2.27 (s, 3H), 2.89-2.98 (m, 1H), 3.14 (dd, A of ABX, $J_{AB}$ = 12.3 Hz, $J_{AX}$ = 8.3 Hz, 1H), 3.23 (dd, B of ABX, $J_{AB}$ = 12.3 Hz, $J_{BX}$ = 6.2 Hz, 1H), 3.53 (brs, 1H), 3.68 (s, 3H), 6.06 (t, *J* = 2.3 Hz, 1H), 6.11 (dd, *J* = 8.1, 2. Hz, 1H), 6.18 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.94-7.00 (m, 4H), 7.15 (t, *J* = 7.7 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 19.8, 21.5, 39.2, 50.9, 55.1, 98.9, 102.5, 106.2, 124.3, 127.4, 128.0, 128.6, 129.9, 138.3, 144.4, 149.5, 160.8;
**HRMS** for $C_{17}H_{22}NO$ $[M+H]^+$: Calcd: 256.1701; Found: 256.1703;

**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 37.8 min (minor), $t_R$ = 47.9 min (major).



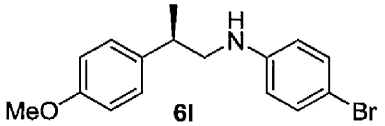

**6j**

*N*-(2-*m*-Tolylpropyl)aniline. The product (32 mg, 56% yield, 80% *ee*) was obtained as a colourless oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.24 (d, $J$ = 7.0 Hz, 3H), 2.27 (s, 3H), 2.89-2.98 (m, 1H), 3.14 (dd, A of ABX, $J_{AB}$ = 12.1 Hz, $J_{AX}$ = 8.3 Hz, 1H), 3.24 (dd, B of ABX, $J_{AB}$ = 12.2 Hz, $J_{BX}$ = 6.2 Hz, 1H), 3.49 (brs, 1H), 6.49 (dd, $J$ = 8.4, 0.9 Hz, 2H), 6.61 (t, $J$ = 7.3 Hz, 1H), 6.96 (t, $J$ = 8.4 Hz, 3H), 7.08-7.12 (m, 2H), 7.14-7.16 (m, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 19.9, 21.5, 39.2, 50.9, 113.0, 117.3, 124.3, 127.4, 128.0, 128.6, 129.3, 138.3, 144.5, 148.2;
**MS** (CI) for $C_{16}H_{20}N$ $[M+H]^+$: *m/z* 226 (100%);
**Anal Calcd** for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 84.71; H, 8.83; N, 6.42.
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 99.5:0.5, flow rate 4 mL/min, λ = 254 nm): $t_R$ = 11.3 min (minor), $t_R$ = 12.3 min (major).




**6k**

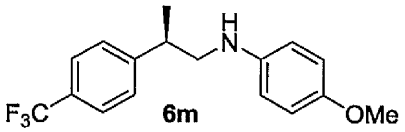
*N*-(2-(4-Methoxyphenyl)propyl)-4-methylaniline. The product (39 mg, 61% yield, 82% *ee*) was obtained as a colourless oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.29 (d, $J$ = 6.9 Hz, 3H), 2.23 (s, 3H), 2.96-3.04 (m, 1H), 3.15 (dd, A of ABX, $J_{AB}$ = 12.2 Hz, $J_{AX}$ = 8.4 Hz, 1H), 3.29 (dd, B of ABX, $J_{AB}$ = 12.2 Hz, $J_{BX}$ = 6.0 Hz, 1H), 3.80 (s, 3H), 6.48-6.51 (m, 2H), 6.85-6.88 (m, 2H), 6.97 (d, $J$ = 8.4 Hz, 2H), 7.12-7.16 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 20.0, 20.4, 38.4, 51.5, 55.3, 113.2, 114.1, 126.5, 128.2, 129.7, 136.6, 145.9, 158.3;
**HRMS** for $C_{17}H_{22}NO$ $[M+H]^+$: Calcd: 256.1701; Found: 256.1700;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98.5:1.5, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 19.9 min (minor), $t_R$ = 22.2 min (major).




**6l**

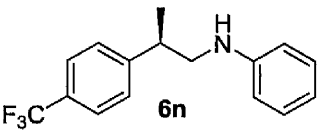
4-Bromo-*N*-(2-(4-methoxyphenyl)propyl)aniline. The product (41 mg, 51% yield, 84% *ee*) was obtained as a pale yellow oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.30 (d, $J$ = 6.9 Hz, 3H), 2.94-3.03 (m, 1H), 3.13 (dd, A of ABX, $J_{AB}$ = 12.2 Hz, $J_{AX}$ = 8.6 Hz, 1H), 3.28 (dd, B of ABX,

$J_{AB}$ = 12.2 Hz, $J_{BX}$ = 6.0 Hz, 1H), 3.80 (s, 3H), 6.41-6.45 (m, 2H), 6.86-6.88 (m, 2H), 7.11-7.14 (m, 2H), 7.20-7.24 (m, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 20.3, 38.7, 51.4, 55.7, 109.2, 114.5, 114.9, 128.5, 132.3, 136.6, 147.5, 158.8;
**HRMS** for $C_{16}H_{19}BrNO$ $[M+H]^+$: Calcd: 320.0650; Found: 320.0659;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 23.0 min (minor), $t_R$ = 27.3 min (major).



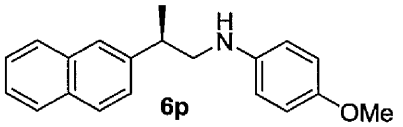
**6m**

4-Methoxy-*N*-(2-(4-(trifluoromethyl)phenyl)propyl)aniline. The product (54 mg, 70% yield, 81% *ee*) was obtained as a colourless oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.34 (d, $J$ = 6.9 Hz, 3H), 3.08-3.17 (m, 1H), 3.22 (dd, A of ABX, $J_{AB}$ = 12.4 Hz, $J_{AX}$ = 8.2 Hz, 1H), 3.33 (dd, B of ABX, $J_{AB}$ = 12.4 Hz, $J_{BX}$ = 6.0 Hz, 1H), 3.75 (s, 3H), 6.52-6.56 (m, 2H), 6.75-6.79 (m, 2H), 7.33 (d, $J$ = 8.1 Hz, 2H), 7.58 (d, $J$ = 8.1 Hz, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 19.5, 39.2, 51.8, 55.8, 114.5, 115.0, 124.3 (q, $J_{CF}$ = 268.9 Hz), 125.6 (q, $J_{CF}$ = 3.6 Hz), 127.8, 128.9 (q, $J_{CF}$ = 21.1 Hz), 141.9, 148.9, 152.3;
**HRMS** for $C_{16}H_{19}BrNO$ $[M+H]^+$: Calcd: 310.1419; Found: 310.1419;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 27.1 min (major), $t_R$ = 29.9 min (minor).



**6n**

*N*-(2-(4-(Trifluoromethyl)phenyl)propyl)aniline. The product (39 mg, 56% yield, 79% *ee*) was obtained as a colourless oil according to the general procedure in 3 d;
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.35 (d, $J$ = 6.9 Hz, 3H), 3.09-3.18 (m, 1H), 3.26 (dd, A of ABX, $J_{AB}$ = 12.6 Hz, $J_{AX}$ = 8.3 Hz, 1H), 3.37 (dd, B of ABX, $J_{AB}$ = 12.6 Hz, $J_{BX}$ = 6.2 Hz, 1H), 3.52 (brs, 1H), 6.56-6.59 (m, 2H), 6.64-6.72 (m, 1H), 7.14-7.19 (m, 2H), 7.33 (d, $J$ = 8.1 Hz, 2H), 7.58 (d, $J$ = 8.1 Hz, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 19.6, 38.6, 50.7, 112.9, 117.6, 125.6 (q, $J_{CF}$ = 3.8 Hz), 127.2 (q, $J_{CF}$ = 289.9 Hz), 127.6, 129.0 (q, $J_{CF}$ = 32.1 Hz), 129.3, 147.7, 148.7;
**HRMS** for $C_{16}H_{17}F_3N$ $[M+H]^+$: Calcd: 280.1313; Found: 280.1707;
**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 29.3 min (minor), $t_R$ = 33.7 min (major).



6p

4-Methoxy-*N*-(2-(naphthalen-2-yl)propyl)aniline.[37] The product (59 mg, 81% yield, 83% *ee*) was obtained as a pale yellow oil according to the general procedure in 3 d;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.41 (d, $J$ = 6.8 Hz, 3H), 3.18-3.26 (m, 1H), 3.29 (dd, A of ABX, $J_{AB}$ = 12.0 Hz, $J_{AX}$ = 8.4 Hz, 1H), 3.39 (dd, B of ABX, $J_{AB}$ = 12.0 Hz, $J_{BX}$ = 5.7 Hz, 1H), 3.74 (s, 3H), 6.52-6.56 (m, 2H), 6.74-6.78 (m, 2H), 7.37 (dd, $J$ = 8.5, 1.7 Hz, 1H), 7.43-7.50 (m, 2H), 7.66 (s, 1H), 7.79-7.83 (m, 3H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 19.9, 39.4, 51.8, 55.8, 114.4, 114.9, 125.5, 125.9, 126.1, 127.6(2), 127.6(4), 128.4, 130.2, 132.5, 133.6, 142.0, 142.3, 152.1;

**HRMS** for $C_{20}H_{22}NO$ $[M+H]^+$: Calcd: 292.1701; Found: 292.1711;

**HPLC** (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): $t_R$ = 36.4 min (major), $t_R$ = 39.3 min (minor).

## 5.6 References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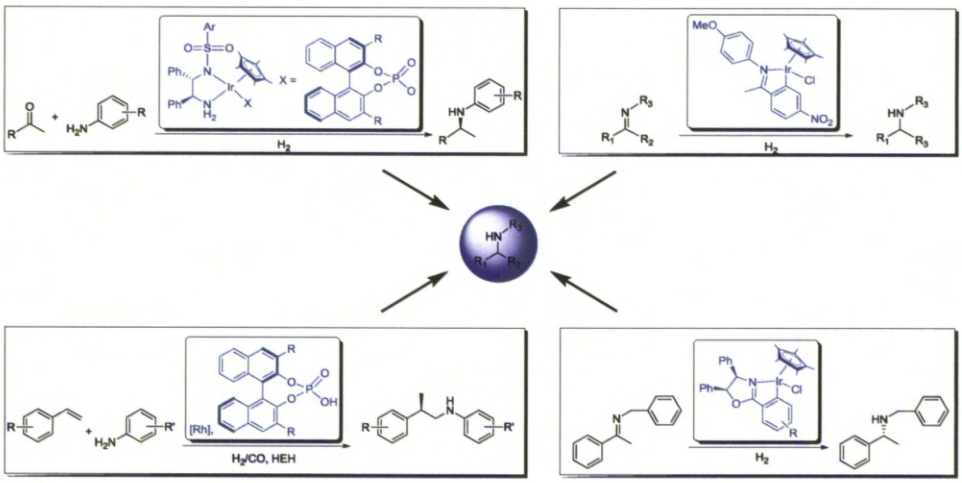
# Chapter 6

## Conclusions and Perspectives

This thesis describes different methodologies for the synthesis of amines, in particular α- and β-chiral amines. Overall, several strategies have been developed, leading to the synthesis of chiral amines, i.e. α-chiral amines from aliphatic ketones, a chiral *N*-benzyl amine and β-chiral amines. These substrates have been historically considered as "challenging", and the literature describing their synthesis is limited. Scheme 1 summarises all the strategies and catalysts developed during this PhD research.




**Scheme 1**: Different strategies for the synthesis of amines developed during this research.

The synthesis of α-chiral amines from aliphatic ketones has been achieved *via* DARA with an Ir-diamine/phosphate complex. The catalytic system is based on the cooperative catalysis of the hydrogen-activating metal cation and a Brønsted acid. The DARA takes place under mild conditions of temperature and pressure, showing excellent yields and enantioselectivities. However, this

methodology had two main challenges: the ineffectiveness of DARA with aliphatic amines, in particular benzylamine; and the poor enantiocontrol for the synthesis of β–chiral amines by DARA of α–branched aldehydes. This prompted us to explore new catalytic systems and pathways to overcome these drawbacks.

The problem in the synthesis of chiral *N*-benzyl amines was then addressed. Initially, achiral cyclometallated iridium complexes were found to be excellent catalysts for imine hydrogenation, presenting high activity and a wide scope of substrates. Chiral analogues of cyclometallated iridium catalysts were subsequently developed, providing enantioselectivity up to 78% *ee* in the hydrogenation of an *N*-benzyl imine.

Finally, a tandem strategy that involves hydroformylation and subsequent reductive amination was proposed for the synthesis of β-chiral amines. Styrene is selectively hydroformylated to the corresponding α-branched aldehyde with a Rh-phosphine catalyst; DARA of this α-branched aldehyde with aromatic amines takes place *in situ*, catalysed by a chiral Brønsted acid. Good yields and enantioselectivities have been obtained. To our knowledge, this is the first example of an asymmetric version of the hydroaminomethylation reaction.

It is hoped that this research work has gone some way towards overcoming the challenges associated with the reduction of imino bonds, but new questions have also emerged. There still exists a need for a 'universal' catalyst that would reduce imino bonds derived from aromatic/aliphatic ketones and aromatic/aliphatic amines. A greener approach for the asymmetric hydroaminomethylation procedure could be achieved by the design of a single

chiral metal catalyst that uses $H_2$ in the imine/enamine reduction step. In addition, Chapter 1 shows that late transition metals have been dominating the area of metal-catalysed asymmetric hydrogenation of imines. An endeavour must be made to search for cheap and non-toxic metal catalysts, which would give rise to more affordable and sustainable methodology.